

University of Alberta

**A placebo controlled, double-blind, randomized clinical trial on the efficacy of
topical diclofenac for temporomandibular degenerative joint disease**

by

Felicia Michele Wilson ©

**A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of**

Master of Science

In

Medical Sciences-Dentistry

Edmonton, Alberta

Fall 2008



Library and
Archives Canada

Published Heritage
Branch

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque et
Archives Canada

Direction du
Patrimoine de l'édition

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence
ISBN: 978-0-494-47441-9
Our file Notre référence
ISBN: 978-0-494-47441-9

NOTICE:

The author has granted a non-exclusive license allowing Library and Archives Canada to reproduce, publish, archive, preserve, conserve, communicate to the public by telecommunication or on the Internet, loan, distribute and sell theses worldwide, for commercial or non-commercial purposes, in microform, paper, electronic and/or any other formats.

The author retains copyright ownership and moral rights in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

AVIS:

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque et Archives Canada de reproduire, publier, archiver, sauvegarder, conserver, transmettre au public par télécommunication ou par l'Internet, prêter, distribuer et vendre des thèses partout dans le monde, à des fins commerciales ou autres, sur support microforme, papier, électronique et/ou autres formats.

L'auteur conserve la propriété du droit d'auteur et des droits moraux qui protègent cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

In compliance with the Canadian Privacy Act some supporting forms may have been removed from this thesis.

Conformément à la loi canadienne sur la protection de la vie privée, quelques formulaires secondaires ont été enlevés de cette thèse.

While these forms may be included in the document page count, their removal does not represent any loss of content from the thesis.

Bien que ces formulaires aient inclus dans la pagination, il n'y aura aucun contenu manquant.

•••
Canada

This is dedicated to my ever patient and loving husband, Jim
&
our boys
who helped me to follow this new path in my life.

Abstract

Patients with temporomandibular degenerative joint disease (TMDJD) may present with pain and limited opening. Literature supports the use of topical diclofenac (Pennsaid®) for symptomatic relief of osteoarthritis of the knee. This study's objective was to investigate the efficacy of Pennsaid® for TMDJD patients. This double-blinded randomized 90 day trial documented pain intensity, voluntary, assisted mouth opening, and amount of acetaminophen used. The short-form Brief Pain Inventory (sf-BPI) and Pain Disability Index (PDI) questionnaires were utilized.

Of the forty-two candidates screened, 28 were eligible that were randomly allotted to either the Pennsaid® or the placebo group. Treatment comprised of application of topical medication (4 drops q.i.d.). Twenty (71.4%) completed the study twelve (42.9%) in the Pennsaid® group, eight (28.6%) in the placebo group.

Calculations revealed no significant change between groups, except for pain intensity, where a significant reduction was seen within the two groups over time. Larger studies are needed.

ACKNOWLEDGEMENTS

The following is a list of people and organizations, with whom this research would not had been possible:

Fund for Dentistry Grant Number 2005-4

Paddlin Labs Inc.

Edmonton Diagnostic Imaging, Edmonton Alberta and Beverly Studer

McNeil Consumer Healthcare, Guelph Ontario, Suppliers of Tylenol®

Strathcona Prescription Centre and Will Leung

Dr. Grant Packota, Oral Maxillofacial Radiologist, University of Saskatchewan

Dr. Paul Major, Department of Orthodontics, University of Alberta

Dr. Pablo Kimos, Department of Orthodontics, University of Alberta

Dr. Ivonne Hernandez, Department of Dentistry, University of Alberta

Dr. Norman Thie, Department of Dentistry, University of Alberta

Dr. Sharon Warren, Department of Rehabilitation Medicine, University of Alberta

TMD/Orofacial Pain Clinic, University of Alberta, especially Jill Dawe

Debbie Dixon, Edmonton Alberta

Vaneeta Grover, Department of Mathematics, Dalhousie University

Wonita Janzen, Department of Rehabilitation Medicine, University of Alberta

Linda Seale, University of Alberta

ccleeland@mail.mdanderson.org.

Behavioral Measurement Database Services (BMDS).

TABLE OF CONTENTS

Chapter 1: Introduction and literature review

1. Introduction	1
1.1 Problem statement	2
1.2 Literature review	3
1.2.1 Temporomandibular degenerative joint disease (TMDJD)	3
1.2.1.1 Epidemiology	5
1.2.1.2 Pathogenesis	6
1.2.1.3 Clinical characteristics	9
1.2.1.4 Radiographic characteristic	9
1.2.1.5 Overview of treatment and management of TMDJD	11
1.2.1.5.1 Conservative treatment	11
1.2.1.5.2 Non-conservative treatment	12
1.2.2 NSAIDS	13
1.2.2.1 Historical overview	13
1.2.2.2 Pharmacokinetics	13
1.2.2.3 Pharmacodynamics	13
1.2.2.4 Side effects and precautions	14
1.2.2.5 Diclofenac	14
1.2.2.6 Cox-2 specific inhibitors	15
1.2.2.7 Topically applied NSAIDS	15
1.2.2.7.1 Dimethyl sulfoxide (DMSO)	17
1.2.2.7.2 Pennsaid®	18
1.2.2.7.2.1 Side effects	19
1.2.2.8 Topical diclofenac and TMDJD	20
1.2.3 Summary	21
1.3 Research questions	21
1.3.1 Additional question	22
1.4 Primary null hypotheses	22
1.4.1 Primary alternate hypotheses	22
1.5 Secondary null hypothesis	22
1.5.1 Secondary alternate hypothesis	23
1.6 References	24

Chapter 2: A placebo controlled, double-blind, randomized clinical trial on the efficacy of topical diclofenac for temporomandibular degenerative joint disease

2.1 Introduction	38
2.2 Methods and materials	39
2.2.1 Subjects	39
2.2.2 Research tools and outcome measures	41
2.2.3 Sample size and subject recruitment	44
2.2.4 Medication dosing	44
2.2.5 Clinical phase and data collection	45
2.2.6 Statistical analysis	49
2.3 Results	50
2.3.1 Efficacy analysis	51
2.3.1.1 Primary outcome efficacy analysis	51
2.3.1.2 Secondary outcome efficacy analysis	52
2.3.1.2.1 Voluntary mouth opening	52
2.3.1.2.2 Assisted mouth opening	53
2.3.1.2.3 Breakthrough analgesic medication	53
2.3.1.2.4 PDI and sf-BPI	54
2.3.1.2.4.1 PDI	54
2.3.1.2.4.2 sf-BPI	54
2.3.1.2.4.2.1 sf-BPI severity subset	54
2.3.1.2.4.2.2 sf-BPI interference subset	55
2.3.2 Intent-to-treat analysis	56
2.3.2.1 Primary outcome intent-to-treat analysis	56
2.3.2.2 Secondary outcomes intent-to-treat analysis	57
2.3.2.2.1 Voluntary mouth opening	57
2.3.2.2.2 Assisted mouth opening	57
2.3.2.2.3 Breakthrough analgesic medication	58
2.3.2.2.4 PDI and sf-BPI	59
2.3.2.2.4.1 PDI	59
2.3.2.2.4.2 sf-BPI	59
2.3.2.2.4.2.1 sf-BPI severity subset	59
2.3.2.2.4.2.2 sf-BPI interference subset	60
2.3.2.3 Tertiary outcomes	60
2.3.2 Post hoc analysis	61
2.3.3 Numbers needed to treat	61
2.4 Discussion	62
2.5 Conclusions	67
2.6 References	69

Chapter 3: General discussion and recommendations

3.1 Overview and clinical implications	76
3.2 Study limitations	76
3.3 Recommendations for future research	78
3.4 References	80
APPENDICES	83

LIST OF TABLES

Table 1.1: Relative and absolute risks of side effects Pennsaid® to oral diclofenac	19
Table 1.2: Relative and absolute risks of side effects Pennsaid® to vehicle control placebo (VCP)	20
Table 2.1: Demographics	51
Table 2.2: Functional pain intensity (mm on 100 mm VAS)	51
Table 2.3: Percent change in functional pain intensity compared to baseline (standard deviation)	52
Table 2.4: Mean and standard deviation in voluntary vertical mouth opening (mm)	52
Table 2.5: Mean and standard deviation in assisted vertical mouth opening (mm)	53
Table 2.6: Average of extra-strength Tylenol® taken for breakthrough analgesia between each time interval	53
Table 2.7: Pain Disability Index scores (mean and standard deviation) at baseline and 90 days	54
Table 2.8: Short form-Brief Pain Inventory severity subset scores (mean and standard deviation) at baseline and day 90	55
Table 2.9: Short form Brief Pain Inventory interference subset (mean and standard deviation) at baseline and day 90	55
Table 2.10: Functional pain intensity (mm on 100 mm on VAS)	56
Table 2.11: Percent change in functional pain intensity (mm) (mean and standard deviation) compared to baseline	57
Table 2.12: Mean and standard deviation for voluntary vertical mouth opening (mm)	57
Table 2.13: Mean and standard deviation for assisted vertical mouth opening (mm)	58

Table 2.14: Average of extra strength Tylenol® taken for breakthrough analgesia between each time interval	58
Table 2.15: Pain Disability Index scores (mean and standard deviation) at baseline and day 90	59
Table 2.16: Short form Brief Pain Inventory severity subset scores (mean and standard deviation) at baseline and day 90	59
Table 2.17: Short form Brief Pain Inventory interference subset (mean and standard deviation) at baseline and day 90	60
Table 2.18: Incidences of side effects	61

ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ANOVA	Analysis of variance between two groups
BMDS	Behavioral Measurements Database Services
BMP-2	Bone morphogenic protein-2
CBCT	Cone beam computed tomography
CHQ-CF 87	Child Health Questionnaire-child form 87
CI	Confidence interval
cm	Centimeters
COX	Cyclooxygenase
CT	Computed tomography
DJD	Degenerative joint disease
DMSO	Dimethyl sulfoxide
EFF	Efficacy analysis
GI	Gastrointestinal
HRQL	Health related quality life
ITT	Intent-to-treat
LBP	Low back pain
LOCF	Last observation carried forward
ml	Milliliter
MRI	Magnetic resonance imaging
n	Number of subjects

NNT	Numbers needed to treat
NSAIDs	Non-steroidal anti-inflammatories
OA	Osteoarthritis
PDI	Pain disability index
PG	Propylene glycol
PG	Proteoglycans
PG2	Vascular prostacyclin
PLO	Poly lecithin organogel
q.i.d.	Four times per day
RA	Rheumatoid arthritis
RDC/Axis II	Research Diagnostic Criteria Axis II
ROA	Radiographic progression of osteoarthritis
SC	Stratum corneum
SD	Standard deviation
sf-BPI	Short form- Brief Pain Inventory
t.i.d.	Three times per day
TMD	Temporomandibular disorders
TMDJD	Temporomandibular degenerative joint disease
TMJ	Temporomandibular joint
VAS	Visual analogue scale
WHO	World Health Organization

Chapter 1

1. Introduction

There are a number of conditions that affect the head and neck that include temporomandibular disorders, headaches, and neuralgias. Under the classification of temporomandibular disorders (TMD), there are several entities. One of these is temporomandibular degenerative joint disease (TMDJD). This is a type of osteoarthritis (OA) which may affect one or both temporomandibular joint(s) (TMJ(s)) (1).

OA is characterized by degeneration of affected joints through inflammation that results in the erosion of cartilage with subsequent loss of joint space, osteophyte formation, and subchondral sclerosis (1-3). The progression has been associated with the integration of genetic influences, local mechanical forces, inflammation and chondrocyte regulation of the extracellular matrix. Sun et al. (4) believe that not only do these factors play a role but also each susceptible individual may have a specific phenotype that is the main contributor to the pathology of OA.

While the disease is in its active phase, there can be a considerable amount of pain that can, in its self, result in a decrease in the affected person's functional ability to chew or open one's mouth.

1.1 Problem Statement

Of the general population, 75% exhibit at least one sign of TMD and 33% will have at least one symptom in their lifetime; however, only 5-6% actually seek treatment (2,5). A 4:1 ratio of females to males seeks treatment for TMD (5). The signs and symptoms are more frequently seen in young adults between the ages of 20 to 40 (5). In this age group TMDJD is evidenced by breakdown and remodeling of the articular surfaces (6). It is believed that this active process lasts between 1 to 1.5 years (7). Of the patients who present with TMD, 8-12% will receive a diagnosis of TMDJD (6,8,9). Since there can be considerable pain and disability associated with the active phase of TMDJD, the treatment is focused on managing symptoms and reducing the time course of the disease. Conservative treatment is advocated through adherence to a soft diet, control of oral habits, limiting mandibular range of movement, glucosamine sulfate (10) and/or the use of oral non-steroidal anti-inflammatories (NSAIDs). However, since a patient's chief complaint is generally related to pain over the TMJ(s) and/or pain on function, the more immediate focus is on pain relief. Patients diagnosed with arthritis are known to be the most frequent users of NSAIDs (11).

Prolonged use of oral NSAIDs increases the risk of upper gastrointestinal (GI) bleeding, and death (12-15). In 1998, 1,322 Canadians died from GI bleeding related to NSAID use. (16) The number of these deaths directly related to arthritis is unknown (16). In the US approximately 107,000 hospitalizations and 16,500 deaths occur each year as a result of NSAID use (16). In addition, increased radiographic progression of OA of the knee

with the prolonged use of NSAIDs has been demonstrated (17,18), and there are concerns of adverse effects on kidney function (1). The latter concern may be related to COX-1 function on renal blood flow (19,20).

Over the past decade newer drugs classified as COX-2 inhibitors were developed that showed up to a 50% reduction in the incidence of gastrointestinal side effects (19-21), and provided similar efficacy to NSAIDs for symptomatic treatment of OA and rheumatoid arthritis (RA) (21). However, cardiovascular events due to their prothrombic properties (19,20) have resulted in most being removed from the market since 2004. With safety concerns of COX-2 inhibitors and known effects of long-term use of oral NSAID utilization, patients are seeking less invasive treatment options. The focus of this research is on the topical application of a NSAID as an alternative to oral (systemic) administration for symptomatic treatment of TMDJD. One such topical, Pennsaid® has been shown to improve function and decreased pain in patients with OA of the knee (22-26), and its efficacy for the symptomatic treatment of TMDJD will be investigated in this clinical research trial.

1.2 Literature review

1.2.1 Temporomandibular joint degenerative joint disease (TMDJD)

The TMJ is a diarthroid structure meaning the intracapsular disc divides the joint into two compartments. The lower compartment allows for rotation while the upper compartment allows for translation. The articular disc is attached to the joint capsule and the condyle. This allows the condyle to rotate under the disc, while maintaining the disc interposed

between the condyle and articular eminence during sliding movement. The sliding of the articular disc is facilitated by the lubricating properties of the synovial fluid.

The synovial membrane is a highly vascularized layer of connective tissue that lines all surfaces of the temporomandibular joint not involved in articulation. Its purpose is to produce and maintain the integrity of the synovial fluid within the joint. The synovial fluid contains phospholipids, proteoglycans, hyaluronic acid and proteins. The connective tissues of the TMJ have the ability to adapt to changes due to function (27). The synovial fluid provides nutrients and lubrication (28) and has mechanisms to provide protection and repair. This may be seen in the form of remodeling (28).

The articular disc consists of fibrous connective tissue and the articular surfaces of the temporal fossa and condylar head are covered with fibrocartilage. This makes the TMJ unique as other joints in the body are lined with hyaline cartilage. The integrity of the fibrocartilage is solely reliant on the synovial fluid (28). As the joint functions, the chondrocytes of the articular fibrocartilage are stimulated to produce the necessary factors required for the up keep and maintenance of the fibrocartilage and the subchondral bone. Some of these factors include collagen and proteoglycans. During the deformation of the articular fibrocartilage, associated with function, fluid is released and absorbed (29). This provides lubrication, which allows the TMJ to move (6). It is the breakdown of the fibrocartilage and changes in the synovial lubrication that contribute to the inability to balance the adaptive process, hence the synovial fluid's protective mechanism becomes lost (30).

1.2.1.1 Epidemiology

TMD has a strong predilection for women in their reproductive years (31-34). Approximately 80% of patients presenting to a TMD/Orofacial clinic are women (35). Between 8-12% of patients who present to such a clinic are diagnosed with TMDJD (6). Degenerative arthritis is the most common form of arthritis affecting the TMJ (1). Radiographic evidence of TMDJD is seen in 14-44% of asymptomatic general population, though the clinical evidence is it affects only 8-16% of the general population (1). Symptoms of TMJ pain are most acute in the young adults (5,36). Anderson (36) could not conclusively state from his study that osseous changes occurred before or after internal disc derangements.

Primary OA is usually seen in an older population, (greater than 50 years of age), (1,2) through radiographic evidence of structural change and remodeling of the condylar surface. Generally patients are asymptomatic but mild discomfort maybe reported (1). It is felt that this is in response to "wear and tear" (30). The theory is mechanical stress and microtrauma contribute to this condition (36). Broussard (30) postulates, "forceful repetitive forces (bruxism) or disk displacement, along with synovial fluid alterations may predispose the elderly individual to OA".

Secondary OA is similar to primary OA but is observed in a younger population; between the ages of 20 - 40 years (1). Symptoms may include joint pain on function, joint stiffness on waking, joint noises and restriction in the range of mandibular movement (1). When clinical presentation and examination suggests the patient may be suffering from

TMDJD, specific radiographs are requested to aid in the diagnosis. The absence of radiographic changes does not entirely mean there is no degeneration, as early in the degenerative process, radiographic evidence may not be seen (34,37,38). Earliest radiographic evidence of structural boney changes is seen as subchondral sclerosis. As the disease progresses, flattening of the condyle, erosion of the cortical plate and osteophyte formations are seen. Bone cysts resulting from the breakdown of the subcortical bone may be observed. Narrowing of the joint space is seen in later stages that may be the result of degenerative changes of the articular head and/or fossa, change in the position of the articular disc or due to adaptive remodeling (28). Post-menopausal women have a greater incidence of knee OA than men (39). This may be due to the presence of estrogen receptors on articular chondrocytes (39-41). Results of Kang's study (41) support a relationship between estrogen receptor polymorphism and pain susceptibility in women between the ages of 17-48 with TMDJD.

1.2.1.2 Pathogenesis of TMDJD

TMDJD is also sometimes referred to as OA of the TMJ. Initiation of TMDJD is thought to be through mechanical loading that has exceeded the adaptive capacity of the joint. The susceptibility of a person to TMDJD is multifactorial attributed to various environmental (28,30) and genetic factors (41). Overloading could be associated with excessive compressive forces or by reduced adaptive capacity of the articular tissue itself (1,28). When the joint's ability to adapt is compromised, there is initiation of a series of molecular events that result in the breakdown of the fibrocartilage of the condylar head of the TMJ (1,28).

All the molecules involved in the pathogenesis of degenerative joint disease of the TMJ have not been identified. However, it is known that the fibrocartilage is dependent on synovial fluid to supply its nutrients and lubrication (28). The lubrication cushions the articular components and absorbs the forces exerted during function (1). The synovial fluid moves during mechanical compression (1). During routine TMJ function, there is balance between the exchange of nutrients and phagocytosis of breakdown products within the synovial fluid (28). When the synovial fluid fails in its function [e.g. during excessive or repetitive function (bruxism)], homeostasis is disrupted, resulting in mechanical failure (1,28). This interrupts the fluidity of rotation and translation of the TMJ. In addition the articular disc may not move as freely, thereby placing increased forces on its attachments that may result in elongation and possibly disc displacement (28). Breakdown of the fibrocartilage, along with change in the make-up of the synovial fluid, may contribute to increased frictional forces (28,30). Proinflammatory cytokines such as interleukin-1B (IL-1B), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-8 (IL-8) are believed involved in the pathogenesis of synovitis OA and internal derangement (42). When these proinflammatory cytokines are released there is interference with the proteoglycans (PG) production.

Collagen fibers and PGs of the articular disc, under normal conditions, form an interwoven network (1). The collagen fiber network is important during compression as it provides resistance and redistribution of forces (1). This network becomes disorganized and eventually fails due to a loss of PGs (3,28).

The synovium provides lubrication to the soft tissues (28). During inflammation there is an increased number of synoviocytes, resulting in an increase in the fluid within the synovial mass (43). This may account for the increase in water, swelling and stiffness reported by patients (43). There is also an increase in water permeability, (29) that 'softens' the articular matrix thus rendering the subchondral bone susceptible to mechanical damage (28). Further overloading of the articular surfaces can occur resulting in further breakdown of the synovial membrane and/or the fibrocartilage. An increase in the destruction of tissue results in increased breakdown products resulting in inflammation. The pain experienced may result from stretched ligaments and/or damage to the subchondral bone (1,28). Damage to the subchondral bone stimulates sensory nerve endings. This causes the release of proinflammatory neuropeptides. The release of the neuropeptides may contribute to tissue damage, inflammation and pain, increased by the release of more cytokines (28).

In healthy cartilage, there is minimal amount of bone morphogenic protein-2 (BMP-2) present. However, during TMJDJD, the BMP-2 concentration is elevated. BMP-2 is believed to be responsible for the induction of the formation of bone and cartilage (44). Higher BMP-2 levels suggest an increase in extracellular matrix production and degradation, which suggest the occurrence of cartilage repair and remodeling (44,45) thus, implying BMP-2's involvement during the initiation of internal derangement and/or pathogenesis of OA changes (46).

With thickening of the articular cartilage, due to the increased forces and adaptation, microfractures may occur (27,47). The result is fragmentation of the articular cartilage and subchondral bone (48). Stiffening of the subchondral bone is believed to be responsible for microfractures of the articular cartilage (47) and its loss during the active phase of OA. With ongoing function, continued loss of articular cartilage results in remodeling and reshaping of the subchondral bone (47,48).

In summary, specific biochemical markers have been identified which include cytokines, proteases, prostaglandins, neuropeptides, isoprotanes, leukotriene, hydroxyl fatty acids and possibly estrogen (41) as playing a role in the initiation and progression of TMDJD. Other factors may include diet, genetic background, psychological stresses and age (1).

1.2.1.3 Clinical characteristics of TMDJD

Patients diagnosed with active TMDJD, typically present with pain and tenderness over the TMJ, restricted mandibular movements, pain on function (chewing, talking, yawning and laughing) and/or have joint sounds. Jaw fatigue, stiffness and tiredness may also be reported. Other symptoms may include head and neck pain, as well as earaches (1,2,49).

1.2.1.4 Radiographic characteristics of TMDJD

Autopsy studies have shown that 40% of the population greater than 40 years of age has some degree of subchondral sclerosis (50-53). Between 14-44% of the general asymptomatic population has radiographic evidence of TMDJD. It has been shown that 5.3% of the general young adult population has TMJ pain and 28.3% have clicking or

crepitus (36,54). Anderson and Katzberg (36) demonstrated a correlation between the severity and incidence of osseous changes to the severity of the internal derangement and clinical progression. Their research involved a study population of 141; mean 26 years of age (range 12-17 years) and the majority of the subjects were female.

The articular disc may be the first component to be affected in the disease process, although dental radiographs such as panoramic imaging will not detect this. The articular disc is best assessed through T2 weighted magnetic resonance imaging (MRI), which provides information on disc morphology (55), but is not ideal for bone assessment (56). T2 weighted MRI may show disc degeneration (myxomatous changes), and the presence of excess amounts of fluid (joint effusion) (57).

Reduced joint space is suggestive of a loss of articular cartilage and/or perforation of the disc, but may not, in itself, be a reliable indicator, as the morphology of the articular surface differs between individuals (1). The osseous integrity and joint space width of the TMJ is best assessed by cone beam CT (CBCT). CBCT has been compared with spiral CT in diagnostic reliability (58).

Loss of cortication of the subchondral cartilage may be an additional early radiographic finding suggestive of TMDJD as a loss of the radiopaque surface of the condyle. As the disease progresses, there is increased radiopacity of the thickened subchondral bony plate (sclerosis). Sclerosis, however, can be an adaptive response to increased or excessive loading of the articular surfaces of the TMJ as observed in the elderly.



Definitive diagnosis of TMDJD is evidenced with osseous degeneration. Panoramic radiographs can identify advanced disease (55), however, cone beam computed tomography (CBCT) and axially corrected tomography are utilized for definitive diagnosis. These later forms of imaging can assess the loss of lamina dura at the point of articular contact subarticular sclerosis, erosions on the surface of the condyle osteophytic lipping and medullary osteolytic lesions.

1.2.1.5 Overview of treatment and management of TMDJD

1.2.1.5.1 Conservative treatment

Self-care instruction is provided for patients presenting with TMD including DJD that includes controlling oral habits (e.g. gum chewing, nail biting), adherence to a soft diet (59) and limiting jaw opening (2). NSAIDs are often used; especially in the presence of pain (1,2). The Rotterdam Study (18) found the most common NSAID in the treatment of OA was naproxen for short-term use (1-30 days) and ibuprofen for long-term use (>180 days). An important outcome of the Rotterdam study was there was a significant association between the long-term use of diclofenac and radiographic progression (ROA) of hip [odds ratio of 2.4 (95% CI 1.0-6.2)] and knee OA [2.7 (95% CI 1.0-8.0)]. This may be due to the interference of diclofenac with cartilage repair and/or with a decrease in pain, patients are subjecting their joints to increased micro/macro trauma (18).

Long-term NSAIDs use may result in additional adverse side effects including GI bleeding (15) and/or acute renal failure (60). Moreover, it has been suggested that some NSAIDS suppress the prostaglandins involved in inflammation, which interferes with proteoglycan synthesis by chondrocytes (18).

This *et al.* (10) have reported that glucosamine sulphate (500mg t.i.d.) is as effective as ibuprofen (800mg t.i.d.) for pain relief and improvement of jaw function in patients with TMJDJD. Glucosamine is a known aminosaccharide found within the human body and used for the biosynthesis of glycosaminoglycans, glycoproteins and proteoglycans (PGs) (61). Bassleer *et al.* (62) showed in vitro that glucosamine sulfate stimulates the amount of PGs synthesized by osteoarthritic chondrocytes, suggesting that they aid in repair mechanisms.

Occlusal stabilization appliances are recommended for patients diagnosed with TMDJD (2). Bruxism may cause further destruction caused by TMJDJ (1). They are shown to be effective in patients with the diagnosis of TMD (2) but the evidence is not as clear for patients with TMDJD and requires further investigation (1,3,59).

1.2.1.5.2 Non-conservative treatment

Occasionally patients do not respond to conservative therapy and intra-articular steroid injections are considered. Surgical interventions such as arthrocentesis and arthroscopy are considered in more refractory cases and in rare cases, where there is considerable destruction of the temporomandibular joint complex, partial or complete joint replacement may be performed (1,2,59).

1.2.2 NSAIDs

1.2.2.1 Historical overview

In 1763, Reverend Edmund Stone described successful treatment of fever with powder derived from bark of a willow. The active ingredient was salicin and when hydrolyzed becomes salicylic acid. Acetylsalicylic acid was first synthesized in 1885 but not used as a medication until 1899. At that time it was considered effective for the treatment of arthritis. The term NSAID was first used in conjunction with phenylbutazone in 1949. Today, the most frequent users of NSAIDs are people with arthritis (16).

1.2.2.2 Pharmacokinetics

NSAIDs are weak organic acids which demonstrate affinity to accumulate in inflamed tissues that have greater acidity. NSAIDs decrease inflammation by inhibiting prostaglandin synthesis by cyclo-oxygenase (COX). COX-1 is present in the gastric mucosa and platelets. The therapeutic effects of anti-inflammation and analgesia are seen through COX-2 while the side effects are linked to COX-1.

1.2.2.3 Pharmacodynamics

NSAIDs inhibit prostaglandin synthesis by inhibiting the release of arachidonic acid, a precursor of prostaglandin (63). With inflammation, COX-2 is induced and leads to swelling and pain (20). COX-2 is an enzyme that is synthesised by inflammatory mediators that are released from granulocytes, basophils and mast cells. Inflammation is reduced through decreasing the release of inflammatory mediators. This results in a decrease in the sensitivity of the blood vessels to bradykinin and histamine. In doing so, the erythema

is reduced due to a reversal of the vasodilatation seen at the site of inflammation. This in turn, affects the t-lymphocytes by decreasing the production of lymphokines.

NSAIDs have the ability to inhibit the prothrombin synthesis, platelet aggregation, act as anti-inflammatories, antipyretic and provide analgesia. They also are known to cause gastric irritation (15) and nephrotoxicity (60).

1.2.2.4 Side effects and precautions

It has been reported that there is a three to ten-fold increase in GI complications and death of patients who regularly take NSAIDs compared to those that do not (64). Hypertension, fluid retention and renal dysfunction are other potential side effects (65). NSAIDs affect prostaglandins that are responsible for vasodilation of the renal blood vessels. Evans *et al.* (60) reported oral NSAIDs were associated with doubling the risk of hospitalization due to acute renal failure. Direct contra-indications for the use of NSAIDs would include patients with a known sensitivity to ASA (65). They are also contraindicated in patients with a history of significant renal impairment, hypertension, congestive heart failure and with active peptic disease (65).

1.2.2.5 Diclofenac

Diclofenac is one of the many NSAIDs indicated for the treatment of osteoarthritis (63). It is widely used due to its analgesic, anti-pyretic, and anti-inflammatories effects (66). The pharmacokinetics and pharmacodynamics are similar to other non-specific NSAIDs.

Diclofenac, as with other NSAIDs, is contraindicated in patients with a history of GI bleeding. The most common side effects for patients who use of oral diclofenac for 3-6 months are gastric or duodenal ulceration and bleeding (1% of patients) (63). Serious GI toxicity can occur with or without symptoms in patients using NSAIDs for a prolonged period of time (14) and GI ulceration and bleeding can occur without warning symptoms (67).

1.2.2.6 COX-2 specific inhibitors

Prolonged use of anti-inflammatories is generally contraindicated. COX-2 specific medications were developed to inhibit COX-2 while not inhibiting COX-1. COX-2 is released into inflamed tissues (20).

Unfortunately more recent clinical trials have demonstrated an increased risk of cardiovascular accidents with COX-2 specific NSAIDS (19,20,68,69). COX-2 inhibitors interfere with the anti- aggregation properties and vasodilation properties of PG₂ (20). Hence, most of these products were taken off the market in the year 2004. Celecoxib remains on the market with a caution against its use in patients with a history of cardiovascular disease.

1.2.2.7 Topically applied NSAIDs

Topically applied medications generally have minimal systemic absorption, thereby adverse effects of systemic administration is avoided. Systematic reviews and met-analyzes have been completed regarding the use of topical NSAIDs for various

conditions. Mason *et al.* has completed reviews of their use for chronic musculoskeletal pain and acute pain (70,71). Moore *et al.* (72) and Tramer *et al.* (73) completed systematic reviews on the use of topical NSAIDs for acute and chronic pain conditions. Studies included within the reviews included transdermal and topical administrative routes (pastes, sprays, gels, creams, patches). Evans *et al.* demonstrated that there are no GI adverse effects associated with topical NSAIDs (15) or increased incidence in renal failure (60). However, there is one case report where a 61-year-old man presented with nephritic syndrome while using two separate topical medications; one tube (100g) contained 5% ibuprofen and the other (100g) contained 3% felbinac were used over ten days (74).

An effective topical medication must be able to penetrate the skin, in particular the stratum corneum (SC), in amounts that are at therapeutic levels (66). Its subsequent diffusion is through the SC into the underlying epidermis, through the dermis and capillary system and into the underlying tissues (75). The SC provides the greatest resistance to penetration (75). The rate of skin permeability varies from person to person (76). The stratum corneum is comprised of keratin-rich cells embedded in multiple lipid bilayers (66). It has been suggested that the higher the skin is hydrated the greater the penetration (75), however, this was not observed by Minghetti (77). Selection of suitable skin penetration enhancers depends on the nature and concentration of the active ingredient in the selected drug (78); the higher the thermodynamic activity, the better the absorption of the drug to penetrate the skin (75). Propylene glycol (PG) is used with oleic

or terpenes to allow greater penetration through the horny layer (75). PG act synergistically with these compounds (75).

Diclofenac sodium alone, as a topical, is not readily absorbed (66). However its ability to penetrate can be improved with the use of enhancers. Ideally an enhancer should be non-allergenic, compatible with the drug and other ingredients, odorless, tasteless, colorless, inexpensive and have good solvent properties (78). It should also not lead to loss of body fluids, electrolytes and the skin should be restored to its original characteristics once the enhancer is removed (78). Different combinations of glycerin/alcohol have been used as solvent systems (79). Modulation of the lipid biosynthesis following the application of a conventional chemical enhancer could potentially further boost the transdermal penetration (80). Such enhancers include DMSO and propylene glycol (75).

1.2.2.7.1 Dimethyl sulfoxide (DMSO)

Dimethyl sulfoxide (DMSO) is a colorless liquid, which is soluble in water, ethanol, and acetone (81). DMSO interacts with keratin of the SC, which enhances its penetration (75). DMSO disrupts the lipid organization of the SC (75). It also alters the protein structure (75). DMSO enhances the transdermal penetration of a variety of drugs (78). Pharmacological properties of DMSO include anti-inflammatory, membrane penetration, analgesia, bacteriostatic and vasodilation (82-85). DMSO has been shown to have therapeutic properties (2,86,87). An article by Calesnick (88) in 1981 indicated that DMSO in concentrations of 50-90% was effective in reducing pain, swelling and muscle spasms. The side effects of DMSO include the presence of garlic taste and odor. This is

believed to be associated with the volatile gas dimethyl sulfide products containing sulfur from the DMSO (26). Localized dermatitis can be seen when used in concentrations of 70-100% (2,87) but is also seen in concentrations of 10% (89,90).

1.2.2.7.2 Pennsaid®

Pennsaid® is a patented topical diclofenac solution (Dimethaid Health Care Ltd in Markham, Ontario). It is a solution that consists of 1.5% diclofenac sodium and 45.5% dimethyl sulfoxide (DMSO) along with propylene glycol (PG), glycerine and alcohol (91).

Towheed's systematic review and meta-analysis (25) of four studies (22-24,26) investigated the efficacy of topical diclofenac in DMSO (Pennsaid®) for OA of the knee. Their results showed that Pennsaid® was effective in reducing pain and improving mobility.

A small amount of diclofenac appears in the urine and plasma after a 1ml topical application of Pennsaid® containing 15mg of diclofenac on the knee (sample size - 4 men) (63). The area of the knee to which the Pennsaid® was applied was washed after 24 hours. Results showed there was more excretion of diclofenac towards the end of the 24 hour period suggesting there is continuous absorption of diclofenac through the skin.

For the treatment of knee OA, Pennsaid® has been shown to have the same efficacy as the maximum daily dose of oral NSAID without the gastric, renal or hepatic side effects

(22-25,91,92). Previous studies involving Pennsaid® for knee OA utilized 10 drops per side of knee, times 4 sides, four times per day. Four millilitres of topical translated into 64mg applied four times per day for a total of 256mg of diclofenac sodium.

1.2.2.7.2.1 Side effects

The most commonly seen side effects in human clinical studies were dermatological reactions including dryness, pruritus and rash (22-24,26).

Table 1.1: Relative and absolute risks of side effects Pennsaid® to oral diclofenac (23,25)

Side Effects	Pennsaid® to Oral Diclofenac Relative Risk	95% CI	Pennsaid® to Oral Diclofenac Absolute Risk (%)
GI			
All GI events	0.72	0.59-0.87	34.7-48.2
Severe GI events	0.35	0.17-0.72	7.4-21.3
Dermatological			
Dry skin	20.8	7.7-55.9	26.7-1.3
Rash	7.2	2.9-18.1	11.6-1.6
Withdrawal - toxicity	0.81	0.61-1.08	20.6-25.4

Table 1.2: Relative and absolute risks of side effects Pennsaid® to vehicle control placebo (VCP) (24-26,91)

Side Effects	Pennsaid® to VCP € Relative Risk	95% CI	Pennsaid® to VCPE Absolute Risk (%)
Localized Adverse Effects			
Dermatological			
Minor dry skin	1.74	1.37-2.22	37.2-21.4
Rash	1.69	0.96-2.95	8.7-5.1
Paraesthesia	0.60	0.33-1.10	4.2-6.8
Systemic Adverse Effects			
GI	1.11	0.74-1.68	12.1-10.8
Any Adverse Effect	1.11	1.0-1.24	68.5-61.5
Withdrawal - toxicity	1.37	0.73-2.56	6.2-4.6

€VCP contains the full carrier with DMSO, no diclofenac sodium.

The long-term safety of Pennsaid® has not been reported and the therapeutic time of use should be limited to three months (93). There is the potential for drug interactions since diclofenac sodium is found in blood samples from subjects in the knee OA studies. Pennsaid® should not be administered if the subject has a history of allergies to NSAIDs (93). Though Pennsaid® has not been clinically associated with GI side effects; its use should be as for oral NSAID administration (93).

1.2.2.8 Topical diclofenac and TMDJD

A search of the Medline database with search terms diclofenac, OA, TMD, TMJ, myofascial pain and topical gel, revealed one clinical trial that compared the use of topical and oral diclofenac in TMD patients (94). The study had a limited sample size (18

subjects per group), short duration (2 weeks), no placebo control group and did not provide any specific diagnosis beyond a diagnosis of TMD. One group was instructed to apply ten drops (16mg/ml diclofenac sodium), four times per day over the affected joint. The concentration of DMSO used was not reported. The topical used in this study was not revealed though it was stated that the patented carrier contained DMSO. The comparison group took 50mg of oral diclofenac twice daily after meals. The results reported were that there was no difference in pain reduction between the topical or orally administrated diclofenac. Three subjects in the topical diclofenac group experienced modest drying at the site of application that resolved once the application was stopped, a result similar to the knee OA studies (22-24,26).

1.2.3 Summary

Current published literature suggests that topical NSAIDs can be effective in reducing pain and improving function of knee OA with minimal side effects. There is a lack of published literature evaluating the efficacy of topical NSAIDs for patients with definitive diagnosis of symptomatic TMDJD and there is no current evidence regarding the efficacy of topical diclofenac (Pennsaid®) for symptomatic TMDJD.

1.3 Research questions

1. Is Pennsaid® more effective than placebo at reducing TMDJD functional pain intensity reported by subjects?
2. Is Pennsaid® more effective than placebo in improving the amount of voluntary and assisted jaw openings in subjects experiencing TMDJD?

3. Is Pennsaid® more effective than placebo for reducing the impact of TMDJD on the patient's quality of life and daily functioning?

1.3.1 Additional question:

If there is pain reduction during treatment, is there a reduction the overall amount of Tylenol® used as breakthrough pain analgesic?

1.4 Primary null hypotheses

1. Pennsaid® does not result in statistically significant reduction of functional pain intensity than placebo in subjects with TMDJD.

1.4.1 Primary alternate hypotheses

1. Pennsaid® results in statistically significant reduction in functional pain intensity than placebo in subjects with TMDJD.

1.5 Secondary null hypothesis

1. Pennsaid® does not result in statistically significant improvement of jaw opening than placebo in subjects with TMDJD.
2. Pennsaid® does not result in statistically significant reduction of the impact of TMDJD in the subject's quality of life and daily functioning.

1.5.1 Secondary alternate hypothesis

1. Pennsaid® results in statistically significant improvement of jaw opening than placebo in subjects with TMDJD.
2. Pennsaid® results in statistically significant reduction of the impact of TMDJD in the subject's quality of life and daily functioning.

References

- (1) Laskin DM, Greene CS, Hylander WL editors. Temporomandibular Disorders: an evidence-based approach to diagnosis and treatment. 1st ed. Chicago: Quintessence Publishing; 2006.
- (2) American Academy of Orofacial Pain, Okeson JP. Orofacial pain: guidelines for assessment, diagnosis, and management. Chicago: Quintessence Pub. Co., Inc.; 1996.
- (3) Orofacial Pain; From Basic Science to Clinical Management The Transfer of Knowledge in Pain Research to Education. Carol Stream, IL: Quintessence Publishing Co, Inc; 2001.
- (4) Sun BH, Wu CW, Kalunian KC. New developments in osteoarthritis. Rheum.Dis.Clin.North Am. 2007 Feb;33(1):135-148.
- (5) Atsu SS, Ayhan-Ardic F. Temporomandibular disorders seen in rheumatology practices: A review. Rheumatol.Int. 2006 Jul;26(9):781-787.
- (6) Kamelchuk LS, Major PW. Degenerative disease of the temporomandibular joint. J.Orofac.Pain 1995 Spring;9(2):168-180.
- (7) Rasmussen OC. Longitudinal study of transpharyngeal radiography in temporomandibular arthropathy. Scand.J.Dent.Res. 1980 Jun;88(3):257-268.
- (8) Toller P. Osteoarthritis of the mandibular condyle. Brit Dent J 1973;134(2):223-231.

- (9) Mejersjo C, Hollender L. Radiography of the temporomandibular joint in female patients with TMJ pain or dysfunction. A seven year follow-up. *Acta Radiol Diagn.* (Stockh) 1984;25(3):169-176.
- (10) Thie NM., Prasad NG, Major PW. Evaluation of glucosamine sulfate compared to ibuprofen for the treatment of temporomandibular joint osteoarthritis: a randomized double blind controlled 3 month clinical trial. *J Rheumatol.* 2001 June 2001;28(6):1347-1355.
- (11) Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. *J.Rheumatol.Suppl.* 1999 Apr;56:18-24.
- (12) Goldstein JL. Who needs prophylaxis of nonsteroidal anti-inflammatory drug-induced ulcers and what is optimal prophylaxis? *Eur.J.Gastroenterol.Hepatol.* 2000 Jun;12 Suppl 1:S11-5.
- (13) Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N.Engl.J.Med.* 1999 Jun 17;340(24):1888-1899.
- (14) Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Arch:Intern.Med.* 1996 Jul 22;156(14):1530-1536.
- (15) Evans JM, McMahon AD, McGilchrist MM, White G, Murray FE, McDevitt DG, et al. Topical non-steroidal anti-inflammatory drugs and admission to hospital for upper

gastrointestinal bleeding and perforation: a record linkage case-control study. *BMJ* 1995 Jul 1;311(6996):22-26.

(16) Health Canada. Arthritis in Canada: An ongoing challenge. 2003:35-49.

(17) Huskisson EC, Berry H, Gishen P, Jubb RW, Whitehead J. Effects of antiinflammatory drugs on the progression of osteoarthritis of the knee. LINK Study Group. Longitudinal Investigation of Nonsteroidal Antiinflammatory Drugs in Knee Osteoarthritis. *J.Rheumatol.* 1995 Oct;22(10):1941-1946.

(18) Reijman M, Bierma-Zeinstra SM, Pols HA, Koes BW, Stricker BH, Hazes JM. Is there an association between the use of different types of nonsteroidal antiinflammatory drugs and radiologic progression of osteoarthritis? The Rotterdam Study. *Arthritis Rheum.* 2005 Oct;52(10):3137-3142.

(19) Mukherjee D. Selective cyclooxygenase-2 (COX-2) inhibitors and potential risk of cardiovascular events. *Biochemical Pharmacology* 2002;63:817-821.

(20) Mukherjee D, Nissen SE, Topol EJ. Risk of Cardiovascular Events Associated with Selective COX-2 Inhibitors. *JAMA* 2001;286(8):954-959.

(21) Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann.Rheum.Dis.* 2003 Dec;62(12):1145-1155.

- (22) Baer P, Williams K, Markus G, Shainhouse JK. A multi-centre, double-blinded, placebo-controlled, clinical trial of diclofenac topical lotion (Pennsaid) in the treatment of the symptoms of primary osteoarthritis of the knee. *Rheumatology* 2001;40(Suppl 1):107.
- (23) Tugwell PS, Wells GA, Shainhouse JZ. Equivalence study of a topical diclofenac solution (pennsaid) compared with oral diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. *J.Rheumatol.* 2004 Oct;31(10):2002-2012.
- (24) Roth SH, Shainhouse JZ. Efficacy and safety of a topical diclofenac solution (pennsaid) in the treatment of primary osteoarthritis of the knee: a randomized, double-blind, vehicle-controlled clinical trial. *Arch.Intern.Med.* 2004 Oct 11;164(18):2017-2023.
- (25) Towheed TE. Pennsaid therapy for osteoarthritis of the knee: a systematic review and metaanalysis of randomized controlled trials. *J.Rheumatol.* 2006 Mar;33(3):567-573.
- (26) Bookman AA, Williams KS, Shainhouse JZ. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. *CMAJ* 2004 Aug 17;171(4):333-338.
- (27) Stegenga B, de Bont LG, Boering G, van Willigen JD. Tissue responses to degenerative changes in the temporomandibular joint: a review. *J.Oral Maxillofac.Surg.* 1991 Oct;49(10):1079-1088.
- (28) Stegenga B. Osteoarthritis of the temporomandibular joint organ and its relationship to disc displacement. *J.Orofac.Pain* 2001 Summer;15(3):193-205.

- (29) Mankin HJ, Thrasher AZ. Water content and binding in normal and osteoarthritic human cartilage. *J.Bone Joint Surg.Am.* 1975 Jan;57(1):76-80.
- (30) Broussard JS,Jr. Derangement, osteoarthritis, and rheumatoid arthritis of the temporomandibular joint: implications, diagnosis, and management. *Dent.Clin.North Am.* 2005 Apr;49(2):327-342.
- (31) Wiberg B, Wanman A. Signs of osteoarthrosis of the temporomandibular joints in young patients: a clinical and radiographic study. *Oral Surg.Oral Med.Oral Pathol.Oral Radiol.Endod.* 1998 Aug;86(2):158-164.
- (32) Dijkgraaf LC, Liem RS, de Bont LG. Synovial membrane involvement in osteoarthritic temporomandibular joints: a light microscopic study. *Oral Surg.Oral Med.Oral Pathol.Oral Radiol.Endod.* 1997 Mar;83(3):373-386.
- (33) Bates RE,Jr, Gremillion HA, Stewart CM. Degenerative joint disease. Part I: Diagnosis and management considerations. *Cranio* 1993 Oct;11(4):284-290.
- (34) Stegenga B, de Bont LG, Boering G. Osteoarthrosis as the cause of craniomandibular pain and dysfunction: a unifying concept. *J.Oral Maxillofac.Surg.* 1989 Mar;47(3):249-256.
- (35) Dworkin SF, Huggins KH, LeResche L, Von Korff M, Howard J, Truelove E, et al. Epidemiology of signs and symptoms in temporomandibular disorders: clinical signs in cases and controls. *J.Am.Dent.Assoc.* 1990 Mar;120(3):273-281.

- (36) Anderson QN, Katzberg RW. Pathologic evaluation of disc dysfunction and osseous abnormalities of the temporomandibular joint. *J.Oral Maxillofac.Surg.* 1985 Dec;43(12):947-951.
- (37) Ericson S, Lundberg M. Structural changes in the finger, wrist and temporomandibular joints. A comparative radiologic study. *Acta Odontol.Scand.* 1968 May;26(2):111-126.
- (38) Holmlund A, Hellsing G. Arthroscopy of the temporomandibular joint: occurrence and location of osteoarthritis and synovitis in a patient material. *Int.J.Oral Maxillofac.Surg.* 1988 Feb;17(1):36-40.
- (39) Bergink AP, van Meurs JB, Loughlin J, Arp PP, Fang Y, Hofman A, et al. Estrogen receptor alpha gene haplotype is associated with radiographic osteoarthritis of the knee in elderly men and women. *Arthritis Rheum.* 2003 Jul;48(7):1913-1922.
- (40) Rosner IA, Goldberg VM, Moskowitz RW. Estrogens and osteoarthritis. *Clin.Orthop.Relat.Res.* 1986 Dec;(213)(213):77-83.
- (41) Kang SC, Lee DG, Choi JH, Kim ST, Kim YK, Ahn HJ. Association between estrogen receptor polymorphism and pain susceptibility in female temporomandibular joint osteoarthritis patients. *Int.J.Oral Maxillofac.Surg.* 2007 May;36(5):391-394.
- (42) Nishimura M, Segami N, Kaneyama K, Suzuki T, Miyamaru M. Proinflammatory cytokines and arthroscopic findings of patients with internal derangement and osteoarthritis of the temporomandibular joint. *Br.J.Oral Maxillofac.Surg.* 2002 Feb;40(1):68-71.

- (43) Goldberg RL, Huff JP, Lenz ME, Glickman P, Katz R, Thonar EJ. Elevated plasma levels of hyaluronate in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheum.* 1991 Jul;34(7):799-807.
- (44) Blaney Davidson EN, Vitters EL, van Lent PL, van de Loo FA, van den Berg WB, van der Kraan PM. Elevated extracellular matrix production and degradation upon BMP-2 stimulation point towards a role for BMP-2 in cartilage repair and remodeling. *Arthritis Res.Ther.* 2007 Oct 8;9(5):R102.
- (45) Fukui N, Zhu Y, Maloney WJ, Clohisy J, Sandell LJ. Stimulation of BMP-2 expression by pro-inflammatory cytokines IL-1 and TNF-alpha in normal and osteoarthritic chondrocytes. *J.Bone Joint Surg.Am.* 2003;85-A Suppl 3:59-66.
- (46) Kaneyama K, Segami N, Nishimura M, Suzuki T, Sato J. Importance of proinflammatory cytokines in synovial fluid from 121 joints with temporomandibular disorders. *Br.J.Oral Maxillofac.Surg.* 2002 Oct;40(5):418-423.
- (47) Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. *Clin.Orthop.Relat.Res.* 1986 Dec;(213)(213):34-40.
- (48) Burr DB, Radin EL. Microfractures and microcracks in subchondral bone: are they relevant to osteoarthritis? *Rheum.Dis.Clin.North Am.* 2003 Nov;29(4):675-685.
- (49) Okeson J, P. Bell's Orofacial Pains: The Clinical Management of Orofacial Pain. 6th ed. Carol Stream, IL: Quintessence Publishing Co, Inc; 2005.

(50) Blackwood HJ. Pathology of the temporomandibular joint. J.Am.Dent.Assoc. 1969 Jul;79(1):118-124.

(51) Blackwood HJ. Vascularization of the condylar cartilage of the human mandible. J.Anat. 1965 Jul;99(Pt 3):551-563.

(52) Oberg T, Carlsson GE, Fajers CM. The temporomandibular joint. A morphologic study on a human autopsy material. Acta Odontol.Scand. 1971 Sep;29(3):349-384.

(53) Stanson AW, Baker HL,Jr. Routine tomography of the temporomandibular joint. Radiol.Clin.North Am. 1976 Apr;14(1):105-127.

(54) Solberg WK, Woo MW, Houston JB. Prevalence of mandibular dysfunction in young adults. J.Am.Dent.Assoc. 1979 Jan;98(1):25-34.

(55) Brooks SL, Brand JW, Gibbs SJ, Hollender L, Lurie AG, Omnell KA, et al. Imaging of the temporomandibular joint: a position paper of the American Academy of Oral and Maxillofacial Radiology. Oral Surg.Oral Med.Oral Pathol.Oral Radiol.Endod. 1997 May;83(5):609-618.

(56) Ohlmann B, Rammelsberg P, Henschel V, Kress B, Gabbert O, Schmitter M. Prediction of TMJ arthralgia according to clinical diagnosis and MRI findings. Int.J.Prostodont. 2006 Jul-Aug;19(4):333-338.

(57) Limchaichana N, Petersson A, Rohlin M. The efficacy of magnetic resonance imaging in the diagnosis of degenerative and inflammatory temporomandibular joint

disorders: a systematic literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;102(4):521-536.

(58) Honda K, Larheim TA, Maruhashi K, Matsumoto K, Iwai K. Osseous abnormalities of the mandibular condyle: diagnostic reliability of cone beam computed tomography compared with helical computed tomography based on an autopsy material. Dentomaxillofac.Radiol. 2006 May;35(3):152-157.

(59) Zakrzewska JM. Assessment and management of orofacial pain. 1st ed. Amsterdam ; Boston: Elsevier; 2002.

(60) Evans JM, McGregor E, McMahon AD, McGilchrist MM, Jones MC, White G, et al. Non-steroidal anti-inflammatory drugs and hospitalization for acute renal failure. QJM 1995 Aug;88(8):551-557.

(61) Braun L, Cohen M. Herbs & Natural Supplements An Evidence-based guide. 1st ed. : Curtis, Vaughan; 2005.

(62) Bassleer C, Rovati L, Franchimont P. Stimulation of proteoglycan production by glucosamine sulfate in chondrocytes isolated from human osteoarthritic articular cartilage in vitro. Osteoarthritis Cartilage 1998 Nov;6(6):427-434.

(63).Hui X, Hewitt PG, Poblete N, Maibach HI, Shainhouse JZ, Wester RC. *In Vivo* Bioavailability and Metabolism of Topical Diclofenac Lotion on Human Volunteers. Pharm Research 1998;15(10):1589-1595.

(64) Sikes DH, Agrawal N, M., Zhao W, W., Kent J, D., Recker D, P., Verburg KM. Incidence of gastroduodenal ulcers associated with valdecoxib compared with that of ibuprofen and diclofenac in patients with osteoarthritis. *European Journal Of Gastroenterology & Hepatology* 2002;14(10):1101.

(65) Drugs And Drugs A Practical Guide to the Safe Use of Common Drugs in Adults. 2nd ed. Canada; 2006.

(66) Nokhodchi A, Sharabiani K, Rashidi MR, Ghafourian T. The effect of terpene concentrations on the skin penetration of diclofenac sodium. *Int J Pharm* 2007;335(1-2):97-105.

(67) Singh G, Triadafilopoulos G. Appropriate choice of proton pump inhibitor therapy in the prevention and management of NSAID-related gastrointestinal damage. *Int.J.Clin.Pract.* 2005 Oct;59(10):1210-1217.

(68) Hedner T, Himmelman A. Cardiovascular complications of COX2 selective inhibitors cause considerable concern. *Bood Pressure* 2004;13:260-261.

(69) Banning M. The use of topical diclofenac for pain in osteoarthritis of the knee: a review. *Br.J.Community Nurs.* 2006 Nov;11(11):487-492.

(70) Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for chronic musculoskeletal pain: systematic review and meta-analysis. *BMC Musculoskelet.Disord.* 2004 Aug 19;5(1):28.

(71) Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for acute pain: a meta-analysis. *BMC Fam.Pract.* 2004 May 17;5(1):10.

(72) Moore RA, Tramer MR, Carroll DP, Wiffen PJ, Mcquay HJ. Quantitive systematic review of topically applied non-steriodal anti-inflammatory drugs. *BMJ* 1998;316:333-338.

(73) Tramer MR, Williams JE, Carroll D, Wiffen PJ, Moore RA, McQuay HJ. Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review. *Acta Anaesthesiol.Scand.* 1998 Jan;42(1):71-79.

(74) Andrews PA, Sampson SA. Topical non-steroidal drugs are systemically absorbed and may cause renal disease. *Nephrol.Dial.Transplant.* 1999 Jan;14(1):187-189.

(75) Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. *Eur.J.Pharm.Sci.* 2001 Sep;14(2):101-114.

(76) Hewitt PG, Poblete N, Wester RC, Maibach HI, Shainhouse JZ. In vitro Cutaneous Disposition of a Topical Diclofenac Lotion in Human Skin: Effect of a Multi-Dose Regimen. *Pharm Research* 1998;15(7):988-992.

(77) Minghetti P, Cilurzo F, Casiraghi A, Montanari L, Fini A. Ex vivo study of transdermal permeation of four diclofenac salts from different vehicles. *J.Pharm.Sci.* 2007 Apr;96(4):814-823.

- (78) Sinha VR, Kaur MP. Permeation enhancers for transdermal drug delivery. *Drug Dev. Ind. Pharm.* 2000 Nov;26(11):1131-1140.
- (79) Lee CK, Uchida T, Kitagawa K, Yagi A, Kim NS, Goto S. Relationship between lipophilicity and skin permeability of various drugs from an ethanol/water/lauric acid system. *Biol. Pharm. Bull.* 1994 Oct;17(10):1421-1424.
- (80) Tsai JC, Guy RH, Thornfeldt CR, Gao WN, Feingold KR, Elias PM. Metabolic approaches to enhance transdermal drug delivery. 1. Effect of lipid synthesis inhibitors. *J. Pharm. Sci.* 1996 Jun;85(6):643-648.
- (81) Pope DC, Oliver WT. Dimethyl sulfoxide (DMSO). *Can. J. Comp. Med. Vet. Sci.* 1966 Jan;30(1):3-8.
- (82) Jacob SW. Dimethyl sulfoxide (DMSO)--current concepts in toxicology, pharmacology, and clinical usefulness in surgery. *Am. Surg.* 1969 Aug;35(8):564-573.
- (83) Backonja M. Introduction to neuropathic pain assessment. 1998.
- (84) Rucker KS. Chronic pain evaluation : a valid, standardized assessment instrument. Boston: Butterworth-Heinemann; 2001.
- (85) Cline ME. Standardization of the visual analogue scale.
- (86) Von Piekartz H, Bryden L. Craniofacial dysfunction and pain : manual therapy, assessment, and management. Oxford ; Boston: Butterworth Heinemann; 2001.

(87) American Academy of Orofacial Pain, McNeill C, American Academy of Craniomandibular Disorders. Temporomandibular disorders : guidelines for classification, assessment, and management. 2nd ed. Chicago: Quintessence Books; 1993.

(88) Calesnick B. Current status of dimethyl sulfoxide (DMSO). Am.Fam.Physician 1981 Apr;23(4):167-168.

(89) Seki H, Fukuda M, Iino M, Takahashi T, Yoshioka N. Immunohistochemical localization of cyclooxygenase-1 and -2 in synovial tissues from patients with internal derangement or osteoarthritis of the temporomandibular joint. Int.J.Oral Maxillofac.Surg. 2004 Oct;33(7):687-692.

(90) Ta LE, Dionne RA. Treatment of painful temporomandibular joints with a cyclooxygenase-2 inhibitor: a randomized placebo-controlled comparison of celecoxib to naproxen. Pain 2004 Sep;111(1-2):13-21.

(91) Baer PA, Thomas LM, Shainhouse Z. Treatment of osteoarthritis of the knee with a topical diclofenac solution: a randomized controlled, 6-week trial [ISRCTN53366886]. BMC Musculoskelet Disord 2005;6:44.

(92) Roth S, Willboroughby D, Maddin S, Vanzeilieghe M, Fraser R. A controlled clinical investigation of 3% diclofenac/2.5% sodium hyaluronate topical gel in the treatment of uncontrolled pain in chronic oral NSAID users with osteoarthritis. Journal: Conference Paper Round Table Series 1995;-(40):132-137.

(93) Compendium of Pharmaceuticals and Specialities. 2007.

- (94) Di Rienzo Businco, L., Di Rienzo Businco, A., D'Emillia M, Lauriello M, Coen Tirelli G. Topical versus systemic diclofenac in the treatment of temporomandibular joint dysfunction symptoms. *Acta Odontol Scand.* 2004;24(5):279-283.

Chapter 2

A placebo controlled, double-blind, randomized clinical trial on the efficacy of topical diclofenac for temporomandibular degenerative joint disease

2.1 Introduction

A number of conditions affect the head and neck that include temporomandibular disorders (TMD). Temporomandibular degenerative joint disease (TMDJD) is an arthritis that may affect one or both temporomandibular joints. TMDJD can create functional jaw pain and decrease the affected person's quality of life (1,2). TMDJD also has a high predilection of occurrence in young females and is generally under recognized in the health care community.

Due to the self-limiting nature of this disease, (24 to 36 months) (1), conservative care is advocated and includes the utilization of systemic non-steroidal anti-inflammatory drugs (NSAIDs). In fact, patients diagnosed with arthritis are the most frequent users of NSAIDs. Prolonged use of oral NSAIDs, however, is known to increase the risk of upper gastrointestinal (GI) perforation and/or bleeding (4-6), and has been associated with a high number of deaths annually in Canada (1,322 deaths in 1998 from GI bleeding) (7). In the United States, it is estimated that 107,000 hospitalizations and 16,500 deaths occur each year as a result of NSAID utilization (8).

Over the last decade or so, newer anti-inflammatory drugs classified as COX-2 inhibitors were developed for relief of symptoms associated with rheumatoid and osteoarthritis

(9,10) and the patients benefited from fewer GI side effects (9,11-14). However, cardiovascular side effects became evident and as a result most have been removed from the market (11). With the relative risks and safety concerns of systemic NSAIDs other administration routes, including topical applications, are being researched for osteoarthritis (OA). One such topical, Pennsaid® (1.5% diclofenac and 45.5% dimethyl sulfoxide [DMSO]) has been reported to be palliative for knee OA without systemic side effects (15-21). There have been no studies on its effectiveness for patients with TMDJD.

The objective of this study was to compare the efficacy of Pennsaid® to placebo in the treatment of painful TMDJD.

2.2 Methods and materials

2.2.1 Subjects

Approval for this study was obtained from Health Canada, the Department of Dentistry and the University of Alberta Human Research Ethics Board (Appendix 2.1 and 2.2).

Recruitment occurred over a ten-month period from Edmonton, surrounding communities and from patients who presented to the University of Alberta, TMD/Orofacial Pain Clinic. Dentists that limited their practice to the treatment of TMD/Orofacial pain within the Edmonton area were contacted by mail. In addition, rheumatologists practicing in the Edmonton area were contacted by mail.

Inclusion Criteria

- A baseline score of ≥ 30 mm on a 100mm measured VAS (Visual Analogue Scale) according to the criteria established by Collins et al. (22) for moderate pain.
- Females from the ages of 18-45 years of age inclusive.
- Primary degenerative joint disease as diagnosed through radiographs utilizing volumetric NewTom computed tomographic images taken in the axial, coronal, and sagittal views assessed by an independent radiologist.

Exclusion Criteria

- Nursing or expectant females or females planning on becoming pregnant.
- Patients having DJD secondarily to trauma, previous infection or general joint/muscle disease.
- Patients who have experience adverse reactions to any of the components of the formulation used in the study.
- Patients who have evidence of periodontal disease, dental caries, oral pathology or infections of the oral cavity.
- Patients with a history of neuropathic pain in the orofacial region.
- Patients scheduled for surgery in the near future.
- Patients currently undergoing orthodontic treatment.
- Patients with a history of epilepsy, cardiovascular disease, renal disease/disorder, hepatic disease/disorder, glaucoma, bowel obstruction, urinary retention, diabetes, hypertension or orthostatic hypotension.
- Patients with a malignancy.

- Patients who are currently using topical preparations for palliative relief for their DJD.
- Inability to understand English.
- Patients who have been wearing an occlusal splint ≤ 3 months.

2.2.2 Research tools and outcome measures

Subjects were assessed at baseline (0), and at 30, 60 and 90 days respectively:

Primary outcome measure

1. Self reported functional pain (pain on chewing, talking, yawning, laughing) utilizing the Visual Analogue Scale, (VAS) (Appendix 2.10).

A 100mm VAS horizontally rectangular measurement plastic device was used to determine the participants' functional pain intensity (Astra Pharma Inc.). The patients were to indicate on the VAS device, their average pain intensity experienced over the past week. Results of Collins et al. study (22) states 30mm or higher on the VAS correlates to moderate pain (22). In order to be able to state that there was clinically significant reduction in pain intensity, there would have to be seen a reduction of 30% on the 100mm VAS from the baseline pain scores (23).

Secondary outcome measures

1. Range of voluntary and assisted inter-incisal vertical jaw opening utilizing a 100mm ruler (Appendix 2.15).

2. Short-form Brief Pain Inventory (sf-BPI) score (Appendix 2.14).

Permission was provided through ccleeland@mail.mdanderson.org for the utilization of the short form Brief Pain Inventory (sf-BPI) questionnaire. The design of the BPI was developed specifically to be used with cancer patients and to measure the intensity of their pain and how it has interfered with their mood, walking and other physical activities, work, social activities, relations with others as well as their sleep. These domains cover the important elements of one's quality of life: the sensory, physical/occupational function, psychological state and sociability. The sf-BPI is divided into two subsets: interference and severity. The interference subset consists of seven questions assessing pain interference with general activity, work, walking ability, relations, sleep, and enjoyment of life. The severity subset consists of four questions assessing pain severity. Both severity, and interference subscales are based on a 0 to 10 numerical scale, with 0 meaning no pain/no interference, and 10 meaning pain as bad as you can imagine/completely interferes. The scoring is done by averaging the severity and interference subscales separately, producing two scores (24).

Keller et al. (25) tested the validity of the BPI in non-cancer pain conditions. His study showed that BPI was valid for OA, rheumatoid arthritis (RA), and lower back pain (LBP). The BPI has been shown to be reliable, responsive and valid, when used with non-cancer patient populations such as AIDS (26).

3. Pain Disability Index (PDI) score (Appendix 2.13).

The pain disability index (PDI) was provided through Behavioral Measurement Database Services (BMDS). It was developed by C.A. Pollard to measure to what extent chronic low back pain interfered with a person's day-to-day activities. It is comprised of seven questions; one for each of the following categories, family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care and life-support activity. The patient rates each of these questions through a graphic rating scale where 0 represented no disability and 10 represented total disability. Tait *et al.* (27) indicate this index can be subdivided into two factors; amount of disability interferes with voluntary activities (questions 1-5 inclusive) and amount of disability interferes with obligatory activities (questions 6 and 7). Though it was tested with patients with chronic pain, it does not appear that the PDI was tested on OA patients.

4. Total amount of Extra-Strength Tylenol® used from baseline (Day 0) to the end of study (Day 90).

Tertiary Outcome Measures

- 1. To compare the adverse effects documented by the Pennsaid® group to those documented by the topical placebo group.**
- 2. To compare reasons for withdrawal from the study between the Pennsaid® group and topical placebo group.**

2.2.3 Sample size and subject recruitment

There were no other clinical studies that had investigated the efficacy of Pennsaid® for the symptomatic treatment of TMDJD. Using 80% power and a 0.05 confidence interval, a sample size of 26 subjects per group was calculated via t-Test for Means Power Tables (28). From studies that involved Pennsaid efficacy on symptomatic relief for knee OA, there was a 10% dropout of subjects from the Pennsaid® group and 20% from the placebo group. Using 20% as the maximum loss of subjects per group, it was determined that an additional 5.2 subjects per group were required in order to maintain the power and confidence. This resulted in a sample size requirement of 62 females.

A randomization code list was computer-generated and privy only to a research assistant.

2.2.4 Medication dosing

The active medication was Pennsaid® (1.5% diclofenac in 45.5% dimethyl sulfoxide [DMSO] solution). The placebo contained only 45.5% DMSO. Both solutions were provided in identical, labeled, 60 ml bottles complete with an included dropper cap (Appendix 2.3 and 2.4). All participants were provided with identical instructions on applying the medication over the affected TMJ four times per day for the study duration.

Extra strength Tylenol® (500mg) was provided for break-through pain and the number of tablets used was recorded in a diary by the subject (Appendix 2.5).

2.2.5 Clinical Phase and Data Collection

This clinical trial was designed to run for a total of 90 days. After the start of the study, follow-up consultation appointments were scheduled for the subjects to return to the clinic every four weeks.

Initial Visit (Screening)

At this screening appointment, written information (Appendix 2.7) regarding the study protocol was reviewed with each potential subject by the main investigator. The main investigator provided any additional information and/or further explanation if required. Once the potential subject had agreed to proceed with the screening appointment in relation to this study, they were provided with an informed consent form (Appendix 2.8) to review. Any questions arising from this form were then answered and once satisfied, the potential subject, witness and main investigator signed the consent form. A copy of the study protocol and signed informed consent was provided to the potential subject.

Once consent was obtained, pretreatment information regarding the subject was collected (Appendix 2.9), including personal information, medical history information, current medications, and data regarding chief complaint (onset, initiating factors, localization, severity, and duration of symptoms, aggravating and alleviating factors). Complete head, neck, TMJ and intra-oral examinations were performed in order to identify any possible pathology related to soft or hard tissues.

Potential subjects were asked to indicate their pain intensity average over the past week using the visual analogue scale (VAS) (Appendix 2.10). Subjects scoring 30mm or greater in the VAS was required.

If the potential subject was considered to be eligible for the study, they were asked to sign, in the presence of a witness, an authorization to contact his/her family physician (Appendix 2.11). This was kept on file until the results from the radiologist were received. These results were discussed at the eligibility visit. The family physician would be contacted if the subject met radiographic and clinical requirements to participate in the study. This was done to assure that there were no medical contraindications (Appendix 2.12). For blinding purposes, the family physician was not informed regarding the group to which the subject was randomly allocated.

A Cone Beam CT scan was performed at initial screening of all clinically eligible subjects. The imaging information was then forwarded to an independent oral and maxillofacial radiologist to interpret.

Eligibility Visit

The purpose of this visit was to review the radiology results and discuss discontinuation of current analgesics (medication wash-out period). A bottle of unopened extra strength Tylenol® (500mg acetaminophen) (Appendix 2.5) was provided for the subject to use as an alternative to their current analgesic. They were instructed that they could take up to 8 tablets of extra-strength Tylenol® per day for breakthrough pain. The previously signed

physician consent form was then faxed to their physician along with information regarding the study and its protocol. Once our research office received the completed physician's consent form, the subject was contacted to start with the 10 day washout of analgesics and future appointments were scheduled.

Baseline Visit (T0)

On completion of the 10day washout period, subjects returned to the clinic. Subjects completed the VAS Pain Scale, Pain Disability Index (PDI) and the short form Brief Pain Inventory (sf-BPI) questionnaires (Appendix 2.13, 2.14). Subjects were then examined to obtain range of voluntary and assisted vertical jaw opening. A monthly diary was provided to the subject to document the daily use of extra strength Tylenol® over the next four weeks. Application of the first dose of topical medication was demonstrated. The subject was then dismissed with a bottle of extra strength Tylenol®, medication diary and a bottle of topical medication.

Second Visit (T1) (Day 30)

Subjects returned in 30 days for data collection using the VAS to measure the functional pain intensity over the past week. A 100mm ruler was used to measure the range of voluntary and assisted vertical jaw opening.

The monthly diary was reviewed to document the daily use of extra strength Tylenol® over the past thirty days and compared to the remainder originally dispensed. The number of milliliters used of the study medication was also recorded. Any adverse reactions were

discussed and documented. This diary was placed in the subject's file as documentation of compliance.

The appointment was ended after the subjects received their study medication, extra strength Tylenol®, the following month's diary along and additional appointment in four weeks time.

Third Visit (T2) (Day 60)

This appointment followed the same protocol as T1.

Fourth Visit (T3) (Day 90)

Data was collected using the functional pain intensity (VAS), voluntary/involuntary mouth openings measurements, Pain Disability Index (PDI) and the Brief Pain Inventory (sf-BPI). The amount of breakthrough pain medications used was recorded based on patient self-report and remaining medication. The number of milliliters of the study medication used was also recorded.

Any notable adverse reactions were discussed and documented. The current signs and symptoms of their TMDJD was discussed and documented. The research assistant broke the randomization code to the subject but not to the main investigator. Where Pennsaid® was effective the subject was provided with a prescription and instructed to continue with the medication. In those cases where Pennsaid® was not effective, other treatment options were discussed by the research assistant.

A letter outlining future treatment recommendations including which study medication the subject was on was sent to their family physician. This letter was completed by one of the senior TMD/Orofacial Pain residents not associated with the research study. Subjects requiring active treatment were offered treatment within the University of Alberta TMD/Orofacial Pain Clinic by one of the residents; not the main investigator.

2.2.6 Statistical analysis

A one-sample Kolmogorov-Smirnov test was used to determine that each dependent variable was normally distributed.

Schwartz and Lellouch put forth the terms "explanatory" or "pragmatic" to describe clinical trials in 1967. (29) Explanatory trials involve the hypothesis of whether or not a treatment effect exists. This term is usually applied to trials that examine biological effects of a specific treatment. Pragmatic trials involve the determination of clinical treatment outcomes. The results from a pragmatic trial are designed to assist in the decision of what treatment should be applied to clinical practice hence making the outcomes more relevant to the 'real' world (30).

The first statistical analysis was performed using the data from subjects who completed the trial. This is referred to as the efficacy (explanatory) analysis (30, 31). Only the data collected from the subjects who completed the 90 day study were considered. A repeated measure ANOVA analysis was completed using the functional pain intensity, voluntary and assisted opening data.

The second statistical analysis used on the data results from this trial was an 'intent-to-treat' (pragmatic) analysis, using the last observation recorded to be carried forward (LOCF). LOCF deals with missing data that occurred due to a subject breaking with protocol through withdrawal or 'lost to follow-up' (31). Lost to follow-up refers to subjects that fail to show for their scheduled appointments.

2.3 Results

A total of 42 candidates were interviewed and clinically screened over a ten-month period. A total of 28 eligible candidates were recruited. A description of the study sample is provided in Table 2.1. Twenty (71.4%) of the subjects completed the study. Of the 20 who completed the study, 12 (42.9%) were allotted to the Pennsaid® group while 8 (28.6%) were to the placebo group.

Of the 8 (28.6%) subjects who failed to complete the study, 6 were from the placebo group and 2 from the Pennsaid® group. In the placebo group, there were 3 subjects who were non-compliant or failed to show for pre-arranged appointments. The other 3 withdrew due to a lack of treatment effect. In the Pennsaid® group 1 subject was lost to follow-up and 1 withdrew due to side effects (altered taste) and lack of effect.

The estimated sample size of 62 determined prior to initiating the study was not met due to lack of qualified candidates.

Table 2.1: Demographics

Female subjects	Pennsaid®	Placebo	Total
Enrolled in the trial	14	14	28
Completed the trial	12	8	20
Drop outs	2 (14%)	6 (42%)	8 (29%)
Intent-to-treat population	14 (100%)	13 (92%)	27 (96%)
Age range (years)	19-44	18-44	18-44
Median age (years)	30.4	28.4	29.4

Though groups were not tested for homogeneity, visual examination of the descriptives, indicated they were similar.

2.3.1 Efficacy analysis

2.3.1.1 Primary outcome efficacy analysis

Descriptive statistics for self reported functional pain intensity are provided in Table 2.2.

Table 2.2: Functional pain intensity (mm on 100 mm VAS)

	Baseline	Day 30	Day 60	Day 90
Pennsaid® n = 12	64.2 (18.7)	49.2 (24.4)	46.3 (21.1)	41.7 (24.5)
Placebo n = 8	53.1 (18.7)	41.3 (24.0)	37.5 (32.3)	30.6 (22.3)

Though there was no difference in the functional pain intensity between the groups [$F(1,19)1.120$ $p=0.304$], there was a significant difference within the two groups $F(1,19)8.75$ $p=0.000$ over time. There was no interaction effect for time $\times$ group [$F(1,19)0.061$ $p=0.980$]. The result of the Bonferroni post hoc analysis indicated there

was a significant difference between the baseline scores and those of Day 60 and Day 90 ($p \leq 0.005$).

In order to consider a change of clinical significance the minimum requirement for clinical significance reduction in pain intensity is 30% of baseline scores (23). Table 2.3 shows that both groups had a decrease of mean functional pain intensity of greater than 30% at Day 90.

Table 2.3: Percent change in functional pain intensity compared to baseline (standard deviation)

Visit	Pennsaid® n=12	Placebo n=8
Day 30	-21.39 (32.17)	-22.29 (39.32)
Day 60	-25.49 (30.10)	-31.00 (52.18)
Day 90	-34.24 (30.76)	-40.54 (37.96)

2.3.1.2 Secondary outcomes efficacy analysis

2.3.1.2.1 Voluntary mouth opening

Descriptive statistics voluntary vertical mouth opening are provided Table 2.4.

Table 2.4: Mean and standard deviation for voluntary vertical mouth opening (mm)

	Baseline	Day 30	Day 60	Day 90
Pennsaid® n = 11	31.5 (7.9)	33.5 (7.2)	34.6 (9.0)	35.0E (7.3)
Placebo n = 8	31.1 (6.2)	30.9 (7.8)	32.1 (3.6)	34.4 (5.7)

EData missing from one of the subjects

ANOVA did not identify a significant difference within the groups for voluntary vertical opening over time, $F(1,18)$ 1.940 $p=0.160$. There was no significant difference between

the groups [$F(1,18)0.296$ $p=0.593$]. There was no interaction effect for time $\times$ group [$F(1,18)0.320$ $p=0.726$].

2.3.1.2.2 Assisted mouth opening

Descriptive statistics for assisted vertical mouth opening are provided in Table 2.5.

Table 2.5: Mean and standard deviation for assisted vertical mouth opening (mm)

	Baseline	Day 30	Day 60	Day 90
Pennsaid® n =11£	40.91 (8.30)	42.36 (8.225)	42.82 (8.554)	43.73 (7.143)
Placebo n=8	39.13 (7.61)	39.00 (7.616)	39.50 (6.761)	39.63 (5.630)

£ Data missing from Day 90 for one of the subjects

ANOVA did not identify a significant difference within the Pennsaid® group and the placebo group over the 90 day period [$F(1,18)1.183$ $p = 0.391$]. There was no significant between group difference in the assisted vertical mouth opening [$F(1,18)0.873$ $p=0.363$]. There was no interaction effect for time $\times$ group [$F(1,18) 0.563$ $p = 0.575$].

2.3.1.2.3 Breakthrough analgesic medication

Descriptive statistics for the number of breakthrough medication used between each time interval are provided in Table 2.6.

Table 2.6: Average of extra strength Tylenol® taken between each time interval

	Day 30	Day 60	Day 90
Pennsaid® n =11	38.5 (47.2)	35.0 (50.0)	28.4 (30.3)
Placebo n=7	38.7 (49.5)	22.8 (21.2)	21.6 (31.2)

There was no statistical significant difference within the groups for the amount of breakthrough medication utilized over time [$F(1,16)1.701$ $p=0.205$]. There was no

interaction between time $\times$ groups [$F(1,16)1.535$ $p=0.231$]. There was no statistical significant difference between the groups [$F(1,16)0.519$ $p=0.482$].

2.3.1.2.4 PDI and sf-BPI

2.3.1.2.4.1 PDI

Descriptive statistics for the pre and post Pain Disability Index scores are shown in Table

2.7.

Table 2.7: Pain Disability Index scores (mean and standard deviation) at baseline and day 90

	Baseline	Day 90
Pennsaid@ n = 12	27.6 (15.8)	22.9 (19.9)
Placebo n= 11	19.6 (9.0)	16.5 (16.7)

Based on ANOVA there was no statistical significant within the pre and post PDI scores for the Pennsaid and placebo groups [$F(1,17)1.992$ $p=0.173$]. There was no interaction between time $\times$ groups [$F(1,16)0.389$ $p=0.540$]. There was no statistical significant difference between the groups [$F(1,16)1.694$ $p=0.207$].

2.3.1.2.4.2 sf-BPI

2.3.1.2.4.2.1 sf-BPI severity subset

Descriptive statistics for the short form – Brief Pain Inventory severity subset scores are provided in Table 2.8.

Table 2.8: Short form-Brief Pain Inventory subset severity scores (mean and standard deviation) at baseline and day 90

	Baseline	Day 90
Pennsaid® n = 12	4.54 (1.83)	4.31 (2.71)
Placebo n= 11	3.54 (1.60)	3.32 (1.86)

Based on ANOVA there was no statistical significant difference within the pre and post sf-BPI subset severity scores for the Pennsaid and placebo groups [$F(1,17)0.676$ $p=0.420$]. There was no interaction between time $\times$ groups [$F(1,16)0.048$ $p=0.829$]. There was no statistical significant difference within groups [$F(1,16)1.780$ $p=0.247$].

2.3.1.2.4.2.2 sf-BPI – subset interference

Descriptive statistics for the short form – Brief Pain Inventory interference subset scores are provided in Table 2.9.

Table 2.9: Short form-Brief Pain Inventory interference subset scores (mean and standard deviation) from baseline to day 90

	Baseline	Day 90
Pennsaid® n = 11	3.89 (2.57)	3.06 (3.13)
Placebo n = 11	2.96 (1.56)	3.03 (2.71)

There was no statistical difference in sf-BPI interference subset over time [$F(1,21)0.849$ $p=0.368$] within the two groups. There was no interaction between time $\times$ groups [$F(1,21)1.302$ $p=0.267$]. There was no statistical significant difference between groups [$F(1,21)0.175$ $p=0.680$].

2.3.2 Intent-to-treat analysis

The intent-to-treat (ITT) population consisted of a total of 27 (96%) subjects (14 Pennsaid® and 13 placebo). A subject was considered to be part of the intent to treat population when once randomized, had evidence of taking at least one dose of the study medication and provided at least 1 follow-up evaluation. One subject in the placebo group presented for the initial visit (baseline) when medication dosing was started and did not return. Since no further data was obtained analysis for this subject was not possible.

2.3.2.1 Primary outcomes intent-to-treat analysis

Descriptive statistics for self reported functional pain are provided in Table 2.10.

Table 2.10: Functional pain intensity (mm on 100 mm VAS)

	Baseline	Day 30	Day 60	Day 90
Pennsaid® n=14	63.6 (20.1)	51.8 (25.0)	49.3 (23.5)	45.4 (26.7)
Placebo n=13	55.8 (18.2)	47.3 (25.1)	45.0 (29.4)	4.8 (25.0)

Though, there was a significant difference in functional pain intensity within the groups over time [$F(1, 26)7.602$ $p=0.001$], there was no significance between the two groups [$F(1, 26)0.410$ $p=0.528$]. There was no interaction effect between time $\times$ group [$F(1,26)0.107$ $p=0.911$]. Post hoc analysis showed a significant change between Baseline and Day 90 over time.

In order to consider a change of clinical significance, the minimum requirement for clinical significant reduction in pain is 30% of baseline scores (23). Table 2.11 shows that

both groups had a decrease of mean functional pain intensity of greater than 30% at the end of the study (day 90).

Table 2.11: Percent change of functional pain intensity (mm) (mean and standard deviation) compared to baseline

	Day 30	Day 60	Day 90
Pennsaid® n =14	-16.4 (32.1)	-20.5 (30.7)	-34.2 (30.8)
Placebo n=13	-15.6 (35.9)	-28.8 (46.7)	-40.5 (38.0)

2.3.2.2 Secondary outcomes intent-to-treat analysis

2.3.2.2.1 Voluntary mouth opening

Descriptive statistics for voluntary vertical mouth opening are provided in Table 2.12.

Table 2.12: Mean and standard deviation for voluntary vertical mouth opening (mm)

	Baseline	Day 30	Day 60	Day 90
Pennsaid® n =14	32.1 (8.4)	33.3 (6.5)	34.2 (8.5)	34.5 (7.2)
Placebo n=13	32.9 (6.6)	32.6 (7.4)	33.2 (4.3)	34.6 (5.3)

ANOVA did not identify a significant difference within the groups for voluntary vertical mouth opening over time [$F(1,26)1.343$ $p=0.270$]. There was no difference between the groups [$F(1,26)0.278$ $p=0.756$]. There was no interaction effect for time $\times$ group [$F(1,26)0.006$ $p=0.941$].

2.3.2.2.2 Assisted mouth opening

Descriptive statistics for assisted vertical mouth opening are provided in Table 2.13.

Table 2.13: Mean and standard deviation for assisted vertical mouth opening (mm)

	Baseline	Day 30	Day 60	Day 90
Pennsaid® n =14	39.86 (8.556)	41.43 (7.663)	41.71 (8.389)	42.43 (7.429)
Placebo n=13	41.15 (7.625)	41.38 (6.911)	41.54 (6.091)	41.62 (5.347)

There was no significant difference in voluntary vertical mouth opening within the groups over time $F(1,26)1.563$ $p=0.220$]. There was no difference between the groups $[F(1,26)0.001$ $p=0.981$]. There was no interaction effect for time $\times$ group $[F(1,26)0.744$ $p=0.478$].

2.3.2.2.3 Breakthrough analgesic medication

Descriptive statistics for the number of tablets of extra- strength Tylenol® used for breakthrough analgesia are provided in Table 2.14.

Table 2.14: Average number of extra strength Tylenol® taken for breakthrough analgesia between each time interval

	Day 30	Day 60	Day 90
Pennsaid® n =14	35.9 (46.3)	35.0 (50.0)	22.6 (29.0)
Placebo n=12	35.5 (48.5)	25.8 (28.1)	26.0 (30.3)

There was no statistical significance difference within the groups for the amount of breakthrough medication utilized over time $[F(1,26)3.108$ $p=0.054$]. There was no statistical significant difference between the groups $[F(1,15)0.020$ $p=0.890$]. There was no interaction between time $\times$ groups $[F(1,15)1.004$ $p=0.374$].

2.3.2.2.4 PDI and sf-BPI

2.3.2.2.4.1 PDI

Descriptive statistics for the Pain Disability Index scores are provided in Table 2.15.

Table 2.15: Pain Disability Index scores (mean and standard deviation) at baseline and day 90

	Baseline	Day 90
Pennsaid® n =14	27.6 (15.8)	23.1 (18.4)
Placebo n=13	19.6 (9.0)	18.0 (16.3)

Based on ANOVA, there was no statistical significant difference within the pre and post PDI scores for the Pennsaid® and placebo groups [$F(1,26)2.072$ $p=0.162$]. There was no interaction effect between time $\times$ groups [$F(1,16)0.470$ $p=0.499$]. There was no statistical significant difference between groups [$F(1,16)1.486$ $p=0.234$].

2.3.2.2.4.2 sf -BPI

2.3.2.2.4.2.1 sf-BPI severity subset

Descriptive statistics for short form – Brief Pain Inventory severity subset scores for baseline and day 90 are provided in Table 2.16.

Table 2.16: Short form-Brief Pain Inventory severity subset scores (mean and standard deviation) at baseline and at day 90

	Baseline	Day 90
Pennsaid® n =14	4.54 (1.83)	4.25 (2.56)
Placebo n=14	3.54 (1.60)	3.39 (1.84)

There was no significant difference in sf-BPI severity subset within the Pennsaid and placebo groups over time [$F(1,27)0.700$ $p=0.410$]. There was no interaction between time

× groups [$F(1,27)0.066$ $p=0.800$]. There was no statistical significant difference between the groups [$F(1,27)1.721$ $p=0.201$].

2.3.2.2.4.2.2 sf-BPI interference subset

Descriptive statistics for the short form – Brief Pain Inventory interference subset scores are provided in Table 2.17.

Table 2.17: Short Form-BPI interference subset scores (mean and standard deviation) from baseline to day 90

	Baseline	Day 90
Pennsaid® n =14	3.89 (2.57)	3.32 (2.91)
Placebo n=14	2.96 (1.56)	3.02 (2.43)

There was no statistical difference within the pre and post scores sf-BPI interference subset scores over time [$F(1,27)0.846$ $p=0.366$]. There was no interaction between time × groups [$F(1,27)1.298$ $p=0.265$]. There was no statistical significant difference between groups [$F(1,27)0.498$ $p=0.487$].

2.3.2.3 Tertiary outcomes analysis

Incidence of side effects

Only one subject withdrew (Day 60) because of side effects citing altered taste and lack of treatment effect (Table 2.18). This subject was from the placebo group. Two (14.3%) other subjects in the placebo group reported taste alteration but indicated it was not serious enough to discontinue the study. Another side effect reported within the placebo group was burning (1[7.1%]). One subject using the placebo reported halitosis and xerostomia. This might have been related to other health concerns that arose during the

study that eventually resulted in this subject discontinuing the study to seek medical treatment. Dry skin was not a documented side effect within the placebo group.

Table 2.18: Incidences of side effects

Side Effects Reported	Pennsaid (n=14)	Placebo (n=14)
Gastrointestinal Reaction		
<i>Nausea</i>	1 (7.1%)	0
Application Site Skin Rx £		
<i>Dry skin</i>	5 (35.7%)	0
<i>Paraesthesia</i>	2 (14.3%)	0
<i>Peeling</i>	2 (14.3%)	0
<i>Burning</i>	3 (21.4%)	1 (7.1%)
<i>Itchy</i>	4 (28.6%)	0
Other Reactions £		
<i>Halitosis</i>	0	1 (7.1%)
<i>Altered Taste</i>	1 (7.1%)	3 (21.4%)
<i>Dizziness</i>	1 (7.1%)	0
<i>Xerostomia</i>	0	1 (7.1%)

£ Some subjects experienced one or more side effects.

2.3.2 Post hoc analysis

Post-hoc power analyzes of the data for functional pain intensity calculated a power of 99% and 98% within the Pennsaid® and placebo groups (EFF, ITT), 6% for the interaction effect of time × group, (the same for EFF and ITT), and 17% and 9% between the two groups. The alpha was set at 0.05.

2.3.3 Number needed treat (NNT)

Using the formula:

$$NNT = \frac{1}{(IMP_{\text{Pennsaid}} / TOT_{\text{Pennsaid}}) - (IMP_{\text{placebo}} / TOT_{\text{placebo}})}$$

IMP Pennsaid® = # of patients treated with Pennsaid® who had > 30% reduction in functional pain intensity

TOT Pennsaid® = total # of patients given Pennsaid® treatment

IMP placebo = # of patients treated with placebo who had > 30% reduction in functional pain intensity

TOT placebo = total # of patients given placebo treatment

$$\text{NNT} = \frac{1}{(7/14) - (6/14)} = 14$$

In order to one patient to experience a clinically significant reduction in functional pain intensity (> 30% reduction) using Pennsaid®, fourteen patients would have to be treated.

2.4 Discussion

TMDJD typically affects young females between the ages of 18 – 45 years. It can be quite debilitating in terms of affecting the ability to open one's mouth and pain on chewing, talking etc. The use of systemic NSAIDs has been documented to be effective in the pain management of patients with TMDJD however long-term use of such medications can result in peptic ulceration and other related GI complications (4-6).

A repeated measures two-way ANOVA analysis was completed using the data obtained from subjects who completed the trial. Lachin (31) refers to this an 'efficacy analysis' defined as "efficacy usually refers to the expected outcome among patients who are able to tolerate the drug, meaning that no dose-limiting side effects such as hepatotoxicity occur; who are adequately compliant ...". There is controversy regarding using this analysis in today's research world as this can result in an underestimated result or effect.

An 'intent-to-treat' analysis involves the analysis of the data collected from all subjects who were randomized in the trial. The analysis therefore includes the data collected from subjects who fail to continue the trial to completion as well as the data collected from the subjects who completed the trial. Incomplete data on this trial's measurement outcomes is

defined as missing data due to failure to attend scheduled appointments (breach in research protocol) and data missing as a result of withdrawal from the trial (regardless of the reason) or failure to collect from the researcher and/or assistant(s). Lachin (31) states these patients continue to be followed with the collection of data provided through the rest of the evaluation appointments. It would be ideal to continue to follow the research subjects throughout the trial in order to be able to perform an ideal intent-to-treat analysis. However, obtaining all the data would be nearly impossible, as they have either withdrawn, failed to follow protocol and/or fail to show up for the scheduled appointments. The method used in this trial to deal with incomplete observations was the Last Observation Carried Forward (LOCF). In this method, the last observation obtained from a subject is substituted for all subsequent missing follow-up observations. An 'intent-to-treat' analysis was used in this trial, dealing with missing data using the LOCF method. Any subjects who, once randomized, had evidence of applying the study medication and provided at least 1 follow-up evaluation were included in the intent-to-treat analysis. Lachin's (31) concern must be kept in mind that there may be a greater possibility of not detecting a positive outcome when using the LOCF compiled data as compared to the data used in an efficacy analysis.

The results showed the efficacy of Pennsaid® and placebo to be similar. There was a decrease in functional pain intensity seen in both groups over time. What caused this decrease in pain is unknown however a number of theories could be postulated. It is possible that pain reduction was independent of the actual treatment. Although temporomandibular disorders will generally improve over time whether treatment is

carried out or not (32, 33), active TMDJD generally has a course of 2-3 years and it is unlikely to reduce significantly over a ninety day time interval. All of the subjects partaking in this trial had been experiencing pain for varying lengths of time and had varying degrees of condylar involvement as a result of the TMDJD. Not all patients seek treatment for TMD and if they do, it may be because of pain. Therefore the initial pain scores might be higher due to this with the subsequent pain measurements decreasing. This is sometimes referred to as 'regression to the mean' (32-34).

Another explanation for pain reduction for both groups could be related to the fact that Pennsaid® and the placebo both contained 45.5% dimethyl sulfoxide (DMSO) as their vehicle to allow penetration through the skin. DMSO has been shown to have therapeutic properties for various health conditions (36-39).

Finally, the most probable explanation for similar pain reduction in the Pennsaid® and placebo groups, relates to the placebo effect or placebo response. If the subject perceives they are obtaining treatment, there are a number of factors that intertwine to contribute to each individual's response. Benedetti (32,34) and Fillingim et al. (33) discuss the external and internal factors that shape the response to treatment. External factors are those that relate to a subject's past experiences thus conditioning the subject to respond a certain way. Verbalization by the researcher may influence the response. Internal factors deals with the subject's expectations, desire for pain relief as well as alteration in memories of past pain experiences (33). Placebo analgesia is another term where the evidence to support its existence is growing (32-35). Evidence suggests a reduction of two

points on the VAS to be associated with placebo effect (34,35), and this reduction has been shown to be clinically significant by Farrar (23).

Though there was no significant change in the number of tablets of extra-strength Tylenol® used for breakthrough analgesia for the two groups over time, a trend was seen showing a decrease in the amount used. This might suggest that as the pain decreased over time, there was less need to use breakthrough analgesic medication.

The goal in clinical research should not be to only investigate clinically significant outcomes of procedure(s) and/or medications measured through the patient's ability to function and a decrease in their pain, but it should look at whether these improvements have any affect on the person's perception of their quality of life. Health is defined by the World Health Organization's (WHO) interpretation of the term is "physical, mental, social well-being not merely the absence of disease or infirmity" (52). Measurement of the health related factors involve determination of a person's well-being related to discomfort, disability and distress. Investigators should assess the effect the clinical outcomes have on the patient's perception of their quality of life.

The health-related quality of life tools must consider what is important to the patient population being studied. Therefore when selecting a health related quality of life (HRQL) tool, details concerning its validity, reliability and responsiveness must be considered, in this case for patients who are diagnosed with TMDJD. An initial literature review, completed in 2005, using the terms HRQL, TMJ, TMD resulted in no references being cited. Since the pain of TMDJD generally lasts more than three months, the pain

can be classified as "chronic". There are many HRQL questionnaires available for a number of other chronic pain entities. For this clinical research project, it was decided to use the short form- Brief Pain Inventory (sf-BPI) (53) and Pain Disability Index (PDI) (54) questionnaires.

There was no difference in the two subset scores (severity and interference) of the sf-BPI or the PDI scores pre- treatment to those obtained at the end of treatment. These questionnaires have been validated and shown to be accurate, reliable and sensitive for a numbers of health conditions, but not in a TMD population. Unfortunately it is unknown if the lack of significant improvement in quality of life and disability was due to lack of effect of the medication or use of the measurement tools not validated for TMD.

There are reports some of the side effects of DMSO include garlic taste and odor (36,37, 40-44). Localized dermatitis can be seen when used in concentrations of 70-100% (38,39) but is also seen in concentrations of 10 % (45-47), which makes it hard to test it against true placebo.

The NNT analysis indicated that 14 subjects would need to be treated with Pennsaid® to have one additional subject experience clinically significant functional pain reduction than just placebo alone. Although the side effects of Pennsaid® were relatively minor, the lack of statistical significant difference between Pennsaid® and Placebo for all the outcome measures and the large number of subjects who need to take the medication for

one subject to have clinically significant pain reduction do not provide justification for routine prescription of Pennsaid for the management of TMDJD.

One of the limitations associated with this research study relates to the small sample size. The 99% and 98% power calculated within the Pennsaid and placebo groups using the functional pain intensity data indicates there was sufficient sample size to detect a significant change within the groups. However, the 17% and 9% power calculated between the Pennsaid® and placebo groups respectively indicates there was insufficient sample size to detect changes in functional pain intensity between the groups. It is possible that there was insufficient sample size to identify statistically significant between group differences for other outcome measures. Visual inspection of the descriptive data suggests that there was a trend toward improved range of jaw opening for both groups. Similarly both groups showed a trend for reduced use of breakthrough analgesic medication, improved quality of life. Multi-center clinical trials would likely provide sufficient sample size in a reasonable time interval. Perhaps the sample that was obtained in this study was not representative of the general population.

The sample obtained in this trial may not be representative of the general population. Not all people with TMDJD present to specialty TMD clinics, private specialty TMD practices or rheumatologists.

Conclusions

There were no statistically significant changes in functional pain intensity, amount of vertical voluntary or assisted opening between the Pennsaid® and the placebo groups.

Both the Pennsaid® and Placebo groups did experience statistically and clinically significant pain reduction over the trial period. A trend was present in the reduction of the amount of extra strength Tylenol® used over the course of this clinical trial. Use of Pennsaid® over placebo alone (45.5% DMSO) for treatment of TMDJD cannot be justified based on the results of this trial.

References

- (1) American Academy of Orofacial Pain, Okeson JP. Orofacial pain: guidelines for assessment, diagnosis, and management. Chicago: Quintessence Pub. Co., Inc.; 1996.
- (2) Laskin DM, Greene CS, Hylander WL editors. Temporomandibular Disorders: an evidence-based approach to diagnosis and treatment. 1st ed. Chicago: Quintessence Publishing; 2006.
- (3) Rasmussen OC. Clinical findings during the course of temporomandibular arthropathy. *Scand.J.Dent.Res.* 1981 Jun;89(3):283-288.
- (4) Sikes DH, Agrawal N, M., Zhao W, W., Kent J, D., Recker D, P., Verburg KM. Incidence of gastroduodenal ulcers associated with valdecoxib compared with that of ibuprofen and diclofenac in patients with osteoarthritis. *European Journal Of Gastroenterology & Hepatology* 2002;14(10):1101.
- (5) Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Arch.Intern.Med.* 1996 Jul 22;156(14):1530-1536.
- (6) Papatheodoridis GV, Sougioultzis S, Archimandritis AJ. Effects of *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs on peptic ulcer disease: a systematic review. *Clin.Gastroenterol.Hepatol.* 2006 Feb;4(2):130-142.
- (7) Health Canada. Arthritis in Canada: An ongoing challenge. 2003:35-49.

- (8) Goldstein JL. Who needs prophylaxis of nonsteroidal anti-inflammatory drug-induced ulcers and what is optimal prophylaxis? *Eur.J.Gastroenterol.Hepatol.* 2000 Jun;12 Suppl 1:S11-5.
- (9) Cannon CP, Curtis SP, Bolognese JA, Laine L. Clinical trial design and patient demographics of the Multinational Etoricoxib and Diclofenac Arthritis Long-Term (MEDAL) Study Program: Cardiovascular outcomes with etoricoxib versus diclofenac in patients with osteoarthritis and rheumatoid arthritis. *American Heart Journal* 2006;152(2):237-245.
- (10) Sun BH, Wu CW, Kalunian KC. New developments in osteoarthritis. *Rheum.Dis.Clin.North Am.* 2007 Feb;33(1):135-148.
- (11) Fitzgerald GA. Coxibs and cardiovascular disease. *N.Engl.J.Med.* 2004 Oct 21;351(17):1709-1711.
- (12) Katzung BG editor. *Basic & Clinical Pharmacology*. 10th ed. Los Altos California: Lange Medical Publications; 2007.
- (13) Mukherjee D. Selective cyclooxygenase-2 (COX-2) inhibitors and potential risk of cardiovascular events. *Biochemical Pharmacology* 2002;63:817-821.
- (14) Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann.Rheum.Dis.* 2003 Dec;62(12):1145-1155.

- (15) Baer P, Williams K, Markus G, Shainhouse JK. A multi-centre, double-blinded, placebo-controlled, clinical trial of diclofenac topical lotion (Pennsaid) in the treatment of the symptoms of primary osteoarthritis of the knee. *Rheumatology* 2001;40(Suppl 1):107.
- (16) Baer PA, Thomas LM, Shainhouse Z. Treatment of osteoarthritis of the knee with a topical diclofenac solution: a randomized controlled, 6-week trial [ISRCTN53366886]. *BMC Musculoskelet Disord* 2005;6:44.
- (17) Bookman AA, Williams KS, Shainhouse JZ. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. *CMAJ* 2004 Aug 17;171(4):333-338.
- (18) Grace D, Rogers J, Skeith K, Anderson K. Topical diclofenac versus placebo: a double blind, randomized clinical trial in patients with osteoarthritis of the knee. *J.Rheumatol.* 1999 Dec;26(12):2659-2663.
- (19) Roth SH. A controlled clinical investigation of 3% diclofenac/2.5% sodium hyaluronate topical gel in the treatment of uncontrolled pain in chronic oral NSAID users with osteoarthritis. *Int.J.Tissue React.* 1995;17(4):129-132.
- (20) Roth SH, Shainhouse JZ. Efficacy and safety of a topical diclofenac solution (pennsaid) in the treatment of primary osteoarthritis of the knee: a randomized, double-blind, vehicle-controlled clinical trial. *Arch.Intern.Med.* 2004 Oct 11;164(18):2017-2023.
- (21) Tugwell PS, Wells GA, Shainhouse JZ. Equivalence study of a topical diclofenac solution (pennsaid) compared with oral diclofenac in symptomatic treatment of

osteoarthritis of the knee: a randomized controlled trial. *J.Rheumatol.* 2004 Oct;31(10):2002-2012.

(22) Collins SL, Moore A, Mcquay HJ. The visual analogue pain intensity scale: what is moderate pain in millimeters? *Pain* 1997;72:95-96.

(23) Farrar JT, Young JP, Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001 Nov;94(2):149-158.

(24) Mendoza TR. Evaluation of the BPI

(25) Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin.J.Pain* 2004 Sep-Oct;20(5):309-318.

(26) Breitbart W, McDonald MV, Rosenfeld B, Passik SD, Hewitt D, Thaler H, et al. Pain in ambulatory AIDS patients. I: Pain characteristics and medical correlates. *Pain* 1996 Dec;68(2-3):315-321.

(27) Tait RC, Chibnall JT, Krause S. The Pain Disability Index: psychometric properties. *Pain* 1990 Feb;40(2):171-182.

(28) Portney LG, Watkins M, P. *Foundations of Clinical Research: Applications to Practice* 2nd ed. Upper Saddle River, N.J.: Pentice Hall Health; 2000.

(29) Schwartz D, Lellouch J. Withdrawals in a therapeutic trial. *Biometrics* 1967 Mar;23(1):135-152.

- (30) McMahon AD. Study control, violators, inclusion criteria and defining explanatory and pragmatic trials. *Stat.Med.* 2002 May 30;21(10):1365-1376.
- (31) Lachin JM. Statistical considerations in the intent-to-treat principle. *Control.Clin.Trials* 2000 Jun;21(3):167-189.
- (32) Benedetti F. Placebo analgesia. *Neurol.Sci.* 2006 May;27 Suppl 2:S100-2.
- (33) Fillingim RB, Price DD. What is controlled for in placebo-controlled trials? *Mayo Clin.Proc.* 2005 Sep;80(9):1119-1121.
- (34) Benedetti F. Mechanisms of Placebo and Placebo-Related Effects across Diseases and Treatments. *Annu.Rev.Pharmacol.Toxicol.* 2007 Jul 31.
- (35) Koshi EB, Short CA. Placebo Theory and Its Implications for Research and Clinical Practice: A Review of the Recent Literature. *Pain Pract* 2007;7(1):4-30.
- (36) Murdoch L. Dimethyl sulfoxide (DMSO)-an overview. *Can.J.Hosp.Pharm.* 1982 May-Jun;35(3):79-85.
- (37) Brown JH. Dimethyl sulfoxide (DMSO)-a unique therapeutic entity. *Aviat.Space Environ.Med.* 1982 Jan;53(1):82-88.
- (38) Brayton CF. Dimethyl sulfoxide (DMSO): a review. *Cornell Vet.* 1986 Jan;76(1):61-90.
- (39) Jacob SW. Dimethyl sulfoxide (DMSO)--current concepts in toxicology, pharmacology, and clinical usefulness in surgery. *Am.Surg.* 1969 Aug;35(8):564-573.

(40) Rosenbaum EE, Jacob SW. Dimethyl Sulfoxide (DMSO) in Musculoskeletal Injuries and Inflammations. II. Dimethyl Sulfoxide in Rheumatoid Arthritis, Degenerative Arthritis and Gouty Arthritis. Northwest Med. 1964 Apr;63:227-229.

(41) Calesnick B. Current status of dimethyl sulfoxide (DMSO). Am.Fam.Physician 1981 Apr;23(4):167-168.

(42) Brown JH. A double-blind clinical study--DMSO for acute injuries and inflammations compared to accepted standard therapy. Curr.Ther.Res.Clin.Exp. 1971 Aug;13(8):536-540.

(43) Brobyn RD. The human toxicology of dimethyl sulfoxide. Ann.N.Y.Acad.Sci. 1975 Jan 27;243:497-506.

(44) Steinberg A. The employment of dimethyl sulfoxide as an antiinflammatory agent and steroid-transporter in diversified clinical diseases. Ann.N.Y.Acad.Sci. 1967 Mar 15;141(1):532-550.

(45) Brown JH. Clinical experience with DMSO in acute musculoskeletal conditions comparing a noncontrolled series with a controlled double blind study. Ann.N.Y.Acad.Sci. 1967 Mar 15;141(1):496-505.

(46) Rubin LF. Toxicity of dimethyl sulfoxide, alone and in combination. Ann.N.Y.Acad.Sci. 1975 Jan 27;243:98-103.

(47) Sulzberger MB, Cortese TA,Jr, Fishman L, Wiley HS, Peyakovich PS. Some effects of DMSO on human skin in vivo. Ann.N.Y.Acad.Sci. 1967 Mar 15;141(1):437-450.

- (48) Jedel E, Carlsson J, Stener-Victorin E. Health-related quality of life in child patients with temporomandibular disorder pain. *Eur.J.Pain* 2007 Jul;11(5):557-563.
- (49) de Lucena LB, Kosminsky M, da Costa LJ, de Goes PS. Validation of the Portuguese version of the RDC/TMD Axis II questionnaire. *Braz Oral Res.* 2006 Oct-Dec;20(4):312-317.
- (50) Reiter S, Eli I, Gavish A, Winocur E. Ethnic differences in temporomandibular disorders between Jewish and Arab populations in Israel according to RDC/TMD evaluation. *J.Orofac.Pain* 2006 Winter;20(1):36-42.
- (51) Segu M, Collesano V, Lobbia S, Rezzani C. Cross-cultural validation of a short form of the Oral Health Impact Profile for temporomandibular disorders. *Community Dent.Oral Epidemiol.* 2005 Apr;33(2):125-130.
- (52) Jenkinson C. *Measuring Health and Medical Outcomes.* London: UCL Press; 1994.
- (53) Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann.Acad.Med.Singapore* 1994 Mar;23(2):129-138.
- (54) Tait RC, Pollard CA, Margolis RB, Duckro PN, Krause SJ. The Pain Disability Index: psychometric and validity data. *Arch.Phys.Med.Rehabil.* 1987 Jul;68(7):438-441.

Chapter 3: General discussion and recommendations

3.1 Overview and clinical implications

Results from this 90 day study revealed a trend showing functional pain intensity decreased, voluntary and assisted opening measurements increased and the amount of extra strength Tylenol® decreased for both treatment groups over time, although not statistically significantly. In addition, the quality of life questionnaires showed no significant differences between the two groups with either of the pre-test or post-test scores. The most common side effect seen in both treatment groups was dry skin at the application site. This was consistent with previous knee OA studies (1-5). The results of this study cannot be projected to the general population as the subjects were obtained from a sample of convenience and not from the general population.

3.2 Study limitations

- 1) Post-hoc power analyzes of the data for functional pain intensity showed a power of 17% and 9% for between the Pennsaid® and placebo groups. Small sample size results in the inability to detect differences between the groups and if the difference or the effect size is small, there needs to be a larger sample size and/or have the study continued for a longer period of time.

It is possible that the concentration of DMSO used in the present study (45.5%) may have been effective in reducing the symptoms of TMDJD and explain why there was a

decrease in functional pain intensity within the both groups with no significant differences recorded between the groups.

- 2) The use of the sf-BPI and PDI as measurement tools for assessing the amount of disability and interference of daily activities may have not been sensitive enough for a TMDJD population since it has not been validated using such a population. The small sample size of this study possibly precluded a more definitive judgment of the sf-BPI and PDI as measurement tools.

A literature search performed December 2007 revisited quality of life tools used for TMD. Appendix 2.17 outlines the results of searching utilizing various terms and combinations. By reviewing the abstracts of some of the articles, other search terms were found which resulted in two separate quality of life assessment tools (RDC/TMD Axis II and Oral Health Impact Profile), which have been validated using TMD populations, (6,7). One of the references with these articles refers to cross-cultural validation using a short form of OHIP for Italian patients with TMD (8). The results from that study stated that patients who were diagnosed with pain showed a larger impact on their quality of life versus patients with no pain. The results using the sf-BPI and PDI showed no differences before or after the current 90 day trial, though a difference in the functional pain intensity was seen. The use of the Oral Health Impact Profile (OHIP) (8) or the RDC/Axis II questionnaires (6,7) may have been more appropriate.

3.3 Recommendations for future research

A multi-center study is recommended to increase the number of participants and decrease study duration. Based on the recruitment rate of 28 patients over 10 months from the current study, a recruitment rate of approximately 24 months is estimated for a single study site. With an adequate sample size, the outcomes studied in this research project could be more confidently recommended. The differences within the group of the TMDJD patients such as severity of the degeneration and if there was difference related to whether one or both joints were affected. Subjects could be assessed and further subdivided as to the severity of the degeneration.

The amount of destruction seen via the cone beam CT scanning could be investigated to determine if there is a correlation between the degrees of joint destruction and Pennsaid® efficacy, and whether having one or both TMJs with active DJD, effects treatment. In addition, clinical and radiographic follow-up over time is recommended to determine if topical anti-inflammatory application alters the natural time course of TMDJD.

The development of a longer acting Pennsaid® which allows for only a once or twice a day application may allow for a better adherence. In addition, changing the placebo to a solution with a clinically insignificant concentration of DMSO may allow for further understanding of the therapeutic responses to DMSO reported in previous studies (9-18). A three armed clinical trial with Pennsaid®, 45.5 % DMSO and placebo (e.g. 5 % DMSO) is suggested. A parallel study using an alternate carrier such a poly lecithin

organogel (PLO) as used in a knee OA study (19) would be of comparative interest and pertinent for patients with TMDJD.

References

- (1) Baer P, Williams K, Markus G, Shainhouse JK. A multi-centre, double-blinded, placebo-controlled, clinical trial of diclofenac topical lotion (Pennsaid) in the treatment of the symptoms of primary osteoarthritis of the knee. *Rheumatology* 2001;40(Suppl 1):107.
- (2) Bookman AA, Williams KS, Shainhouse JZ. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. *CMAJ* 2004 Aug 17;171(4):333-338.
- (3) Roth SH, Shainhouse JZ. Efficacy and safety of a topical diclofenac solution (pennsaid) in the treatment of primary osteoarthritis of the knee: a randomized, double-blind, vehicle-controlled clinical trial. *Arch.Intern.Med.* 2004 Oct 11;164(18):2017-2023.
- (4) Towheed TE. Pennsaid therapy for osteoarthritis of the knee: a systematic review and metaanalysis of randomized controlled trials. *J.Rheumatol.* 2006 Mar;33(3):567-573.
- (5) Tugwell PS, Wells GA, Shainhouse JZ. Equivalence study of a topical diclofenac solution (pennsaid) compared with oral diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. *J.Rheumatol.* 2004 Oct;31(10):2002-2012.
- (6) Reiter S, Eli I, Gavish A, Winocur E. Ethnic differences in temporomandibular disorders between Jewish and Arab populations in Israel according to RDC/TMD evaluation. *J.Orofac.Pain* 2006 Winter;20(1):36-42.

- (7) de Lucena LB, Kosminsky M, da Costa LJ, de Goes PS. Validation of the Portuguese version of the RDC/TMD Axis II questionnaire. *Braz Oral Res.* 2006 Oct-Dec;20(4):312-317.
- (8) Segu M, Collesano V, Lobbia S, Rezzani C. Cross-cultural validation of a short form of the Oral Health Impact Profile for temporomandibular disorders. *Community Dent. Oral Epidemiol.* 2005 Apr;33(2):125-130.
- (9) John H, Laudahn G. Clinical experiences with the topical application of DMSO in orthopedic diseases: evaluation of 4180 cases. *Ann.N.Y.Acad.Sci.* 1967 Mar 15;141(1):506-516.
- (10) Brown JH. Dimethyl sulfoxide (DMSO)--a unique therapeutic entity. *Aviat.Space Environ.Med.* 1982 Jan;53(1):82-88.
- (11) Brown JH. A double-blind clinical study--DMSO for acute injuries and inflammations compared to accepted standard therapy. *Curr.Ther.Res.Clin.Exp.* 1971 Aug;13(8):536-540.
- (12) Jacob SW, Bischel M, Herschler RJ. Dimethyl Sulfoxide (DMSO): a New Concept in Pharmacotherapy. *Curr.Ther.Res.Clin.Exp.* 1964 Feb;6:134-135.
- (13) Jimenez RA, Willkens RF. Dimethyl sulfoxide: a perspective of its use in rheumatic diseases. *J.Lab.Clin.Med.* 1982 Oct;100(4):489-500.

- (14) Steinberg A. The employment of dimethyl sulfoxide as an antiinflammatory agent and steroid-transporter in diversified clinical diseases. *Ann.N.Y.Acad.Sci.* 1967 Mar 15;141(1):532-550.
- (15) Calesnick B. Current status of dimethyl sulfoxide (DMSO). *Am.Fam.Physician* 1981 Apr;23(4):167-168.
- (16) David NA. The pharmacology of dimethyl sulfoxide. *Annu.Rev.Pharmacol.* 1972;12:353-374.
- (17) Jacob SW. Dimethyl sulfoxide (DMSO)--current concepts in toxicology, pharmacology, and clinical usefulness in surgery. *Am.Surg.* 1969 Aug;35(8):564-573.
- (18) Pope DC, Oliver WT. Dimethyl sulfoxide (DMSO). *Can.J.Comp.Med.Vet.Sci.* 1966 Jan;30(1):3-8.
- (19) Grace D, Rogers J, Skeith K, Anderson K. Topical diclofenac versus placebo: a double blind, randomized clinical trial in patients with osteoarthritis of the knee. *J.Rheumatol.* 1999 Dec;26(12):2659-2663.

- 83 -

APPENDICES

2.1 Health Canada Approval

10. 2006 1:23PM
Canada Canada

HEALTH CANADA (SMAB)
Canada

NO. 394 P. 1
Therapeutic Products Directorate
2nd Floor, Holland Cross, Tower A
Address Locator 3002C
OTTAWA, Ontario
K1A 0K9

For file Your reference

Our file Your reference

10 January 2006

9427-U0180-77C

Dr. Michele Wilson
Resident
TMD/Orofacial Pain Investigation Unit,
Department of Dentistry
University of Alberta
4068 Dentistry/Pharmacy Centre
EDMONTON, Alberta
T6G 2N8

ACKNOWLEDGEMENT CLINICAL TRIAL APPLICATION

RE: PROTOCOL# 5935

Dear Dr. Wilson:

This will confirm the receipt on January 6, 2006, of your information and material to support a Clinical Trial Application (CTA) for PENNSAID, control number 103090. You are requested to refer to the file number and control number in any communication relating to this application.

Please note that additional information may be requested during the review stage.

You are reminded that under paragraph C.05.006 (1) (b) of the Food and Drug Regulations, the sale of a new drug for clinical testing is prohibited if, within 30 days after the date of receipt of the submission, the Director has sent a notice by registered mail that the Clinical Trial Application is not satisfactory.

Yours sincerely,

Paul van der Voort

For

Lynne McVeigh
Submission Management Unit
Senior Medical Advisor Bureau

LM/ps

Canada

2.2 University of Alberta Health Research Ethics Board Approval

Health Research Ethics Board

215 Thomas Medical Research Centre
University of Alberta, Edmonton, Alberta T6C 2G2
p. (780) 922-8225 (Biomedical Panel)
p. (780) 922-8822 (Health Panel)
p. (780) 922-8229
p. (780) 922-8829
t. (780) 445-5900

ETHICS APPROVAL FORM

Date: June 2005

Name(s) of Principal Investigator(s): Dr. Norman Thie

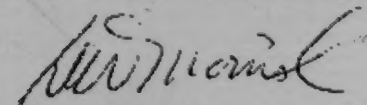
Department: Dentistry

Title: Double-blind randomized clinical study on topical Diclofenac gel efficacy in symptomatic relief of temporomandibular degenerative joint disease in women

The Health Research Ethics Board (Biomedical Panel) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation.

Specific Comments:

The Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. Subject consent for access to identifiable health information is required for the research described in the ethics application, and appropriate procedures for such consent have been approved by the REB Panel. The REB has also reviewed and approved the patient information material and consent form.



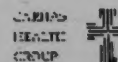
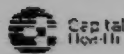
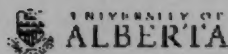
D. W. Morrish, M.D.
Chairman, Health Research Ethics Board
Biomedical Panel

APR - 5 2006

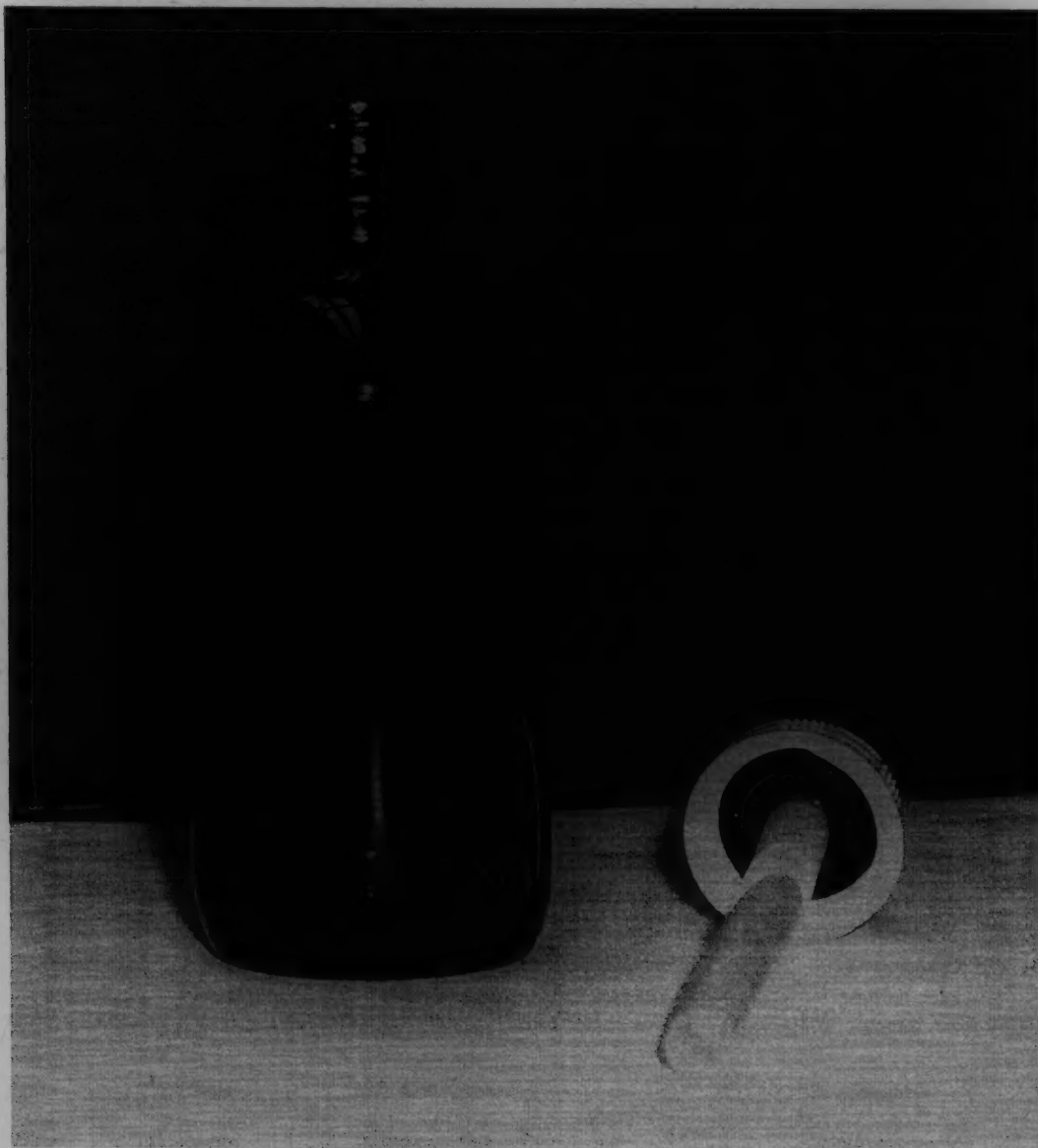
Date of Approval Release

This approval is valid for one year

FORM 45035



2.3 Trial Medication Dispensing Bottle with Cap



2.4 Trial Medication Label

Dr. Michele Wilson, 2006

Double-blind Randomized Clinical Study o Topical Diclofenac (Pennsaid) Efficacy versus Placebo in Symptomatic Relief of Temporomandibular Degenerative Joint Disease (TMDJD)

Pennsaid (Diclofenac) = Spreadsheet code: G

Office (780) 492-2300 Pager: 431-6322

P Code: DIN 02247265 (1.5%mg / 360ml)

Exp.Date: 03-2008 Control# 103090

Store at room temperature (15° to 30° C)

PMS Lot#G60340DE Control/Pennsaid (Diclofenac)

Random Code: _____ Take as directed

Control/Placebo = T2 - Spreadsheet code: F

Office (780) 492-2300 Pager: 431-6322

P Code: DIN 12042006 (1.5 mg / 360ml)

Exp.Date: 03-2008 Control# 103090

Store at room temperature (15° to 30° C)

PMS Lot# F04588635 Control/Pennsaid (Diclofenac)

Random Code: _____ Take as directed

INVESTIGATIONAL DRUG TO BE USED BY QUALIFIED

INVESTIGATOR ONLY /DROGUE DE RECHERCHE -

RESERVEE UNIQUEMENT A L'USAGE DE CHERCHEURS COMPETENTS.



Faculty of Medicine & Dentistry-TMD/Orofacial Pain Clinic

INVESTIGATIONAL DRUG TOBE USED BY QUALIFIED

INVESTIGATOR ONLY/ DROGUE DE RECHERCHE -

RESERVEE UNIQUEMENT A L'USAGE DE CHERCHEURS COMPETENTS

2.5 Extra strength Tylenol® 500mg



2.6 Daily Journal



UNIVERSITY OF
ALBERTA

Department of Dentistry
Faculty of Medicine and Dentistry

Dentistry and Dental Hygiene -- Excellence in Dental Health
Dentistry/Pharmacy Centre
Edmonton, Alberta, Canada T6G 2N8

Double-blind Randomized Clinical Study on Topical Diclofenac Gel Efficacy versus Placebo in Symptomatic Relief of Temporomandibular Degenerative Joint Disease (TMDJD)

Please bring this diary with you to every appointment.

You have been given acetaminophen for you to use when you are in pain. The maximum amount of acetaminophen (Tylenol®) you can take in a day is 4000 mg.

This equals a total of eight (8) tablets.

Please record the amount of Tylenol that you used each day. This is very important to the success of this study.

Studies have shown that there have not been any serious side effects from the use of topical medication.

However, it is very important to keep a record of any side effects that you do experience.

The attached sheet is for you to record the amount of acetaminophen that you have taken each day and any side effects that you experience.

If you have questions or concerns, please do not hesitate to contact the TMD/Orofacial Pain Clinic at (780) 492-2700

Double-blind Randomized Clinical Study on Topical Diclofenac Gel Efficacy versus Placebo in Symptomatic Relief of Temporomandibular Degenerative Joint Disease (TMDJD)

Patient Name: _____ **Study No:** _____

Date	Number of AM	Acetaminophen PM	Note any changes of the skin where topical is applied
Total used			

Verified by: _____ **Date:** _____

Please bring this diary with you to every appointment.

2.7 Protocol Information Provided to Potential Subject

UNIVERSITY OF
ALBERTA

Department of Dentistry
Faculty of Medicine and Dentistry

Dentistry and Dental Hygiene -- Excellence in Dental Health
Dentistry/Pharmacy Centre
Edmonton, Alberta, Canada T6G 2N8

Double-blind Randomized Clinical Study on Topical Diclofenac Efficacy versus Placebo in Symptomatic Relief of Temporomandibular Degenerative Joint Disease (TMDJD)

Primary Investigators	Phone
Dr. Norm Thie, Clinical Director, TMD/Orofacial Pain Clinic	(780) 492-9906 or (780) 492-2300
Dr. Michele Wilson, TMD/Orofacial Pain Resident, TMD/Orofacial Pain Clinic	(780) 492-6895 or (780) 492-2300

Background:

Many people have jaw pain that is related to arthritis of their jaw joint(s). This condition is called temporomandibular degenerative joint disease which is osteoarthritis of the TMJ (temporomandibular joint). Many treatments are being used to treat this disease such as medications and splint therapy. Many of the medications used have unhealthy side effects such stomach problems or cause an increase in your chance to have a stroke or heart attack. Because of this, researchers and patients are looking for safer medications to help decrease the pain. Topical medications soak into the skin therefore they do not have to be swallowed to work. This way the medication is put where you need it and should work where you need it without having to go through your whole body.

A certain type of topical medication has been shown to decrease pain in people with arthritis of the knee(s). However, there have been no studies to show that this is true for arthritis of the TMJ. This is the reason why our researchers want to study this type of medication.

Purpose:

Dental researchers here at the university are working with people who have been told they have arthritis of their jaws. If you are having pain in your jaw we are trying to find out if the use of a specific topical medication (diclofenac) will help decrease your pain and maybe make you use your jaw better.

Procedures: Participating in this study will involve:

- a) Visiting the TMD/Orofacial Pain Clinic for a total of 6 appointments. Each appointment will last approximately 20-30 minutes.
- b) You will be randomized (like flipping a coin) to receive any of the two of treatments: drug a 0.2 cc 4 times per day; or placebo (an inactive substance) 0.2 cc 4 times per day. Neither you nor your physician can choose or know which treatment you are receiving. This "blinding" is necessary to fairly test these drugs. In an emergency, your physician can immediately find out which of the drugs/treatments you are receiving.

c) When you agree to help in this study, you will expect:

1. Someone from the TMD/Orofacial Pain Clinic at the University of Alberta will telephone you to explain how the study works. They will ask you a few questions to see if you are eligible. If you are eligible, we will make an appointment for you to come into the clinic to have a head and neck check-up. You will be given \$2.00 to help pay for parking at the University.
2. On your first appointment, you will be given the information about the study to read. If you agree to take part in this study, we will ask you to sign a consent form. We also ask your permission to contact your family doctor to obtain your chart so that we can be sure you will be safe applying the medication. We will do a 10-15 minute check-up to check the inside of your mouth, see how far you can move your jaw and check your jaw joints. If this check-up shows that you can take part in the study, and you are interested in going ahead with using a topical medication, we will make another appointment for you. If you have not had recent x-rays done at Edmonton Diagnostic Center we will make you an appointment to have special x-rays taken. Once we receive the findings of these x-rays, we will know if you can continue in this study. While waiting for these results, your family doctor will be contacted to make sure that it is safe for you to use the medication. We will contact you to let you know one way or the other and if so, we will ask you to stop taking any pain medication for 10 days before your next appointment. It is very important that you are not on any pain medications when you start this study. If you are not eligible to take part in this study, we will discuss other treatment options that are available for you.
3. Your second appointment will take about 25 to 30 minutes. We ask that you tell us how much pain you are feeling and ask you to answer a few questions about how the pain affects your life. We will also do another check-up to measure how well you can open and move your jaw today.
 - You will be put into one of two groups. You will be given either topical diclofenac or a placebo. You will be given a supply of Tylenol® that you can take if you have pain.
 - The research assistant will carefully explain to you how you are to use the medication. You will be given forms to take home to record the amount of Tylenol® you are taking. There is room for you to write anything unusual you noticed when using the medication.
 - Besides the study medication and the Tylenol® you are not allowed to take any other medications or treatments for pain. Failure to follow this information will ruin the results. You must tell us if there are changes in your other medications or over-the-counter medications.
4. You will be asked to come back to the clinic three more times. Each of these visits will take 25 to 30 minutes. Your next visit will be 30 days after you start using the ointment. The second visit will be 60 days after you started. The third and final will be after 90 days. Each visit will be pretty much the same: the research assistant will ask you about your pain. We will do a jaw exam every time. We will count the number of Tylenol® tablets you have left and will give you enough Tylenol® and cream to last you until your next visit.
5. At this time, we will do the final checkup. We will ask you about your pain, and how it is affecting your life.
6. During the study, a research assistant will telephone you once every two weeks to see if you are having any pain. They will also ask if you are having any problems. Please make sure that you fill out your forms. Have them handy to the telephone for when the

assistant calls you. If you have undesirable problems or excessive pain, please call the research assistant or the TMD/Orofacial Pain Clinic at (780) 492-2300 or the pager number provided.

7. When the study is finished, you will be told which medication you were using. We will write a letter to your family doctor about how well the medication worked for you. We will let the doctor know what we recommend for your pain.

Possible Benefits:

The medication applied during this study may help decrease your pain and improve the use of your jaw. It may improve your quality of life. You may learn more about your pain condition. You will be helping us to understand how to treat others with your condition.

Possible Risks:

There may be irritation where you apply the medication to the skin. Past studies have shown that this irritation goes away quickly when you stop applying the medication. There could be other side-effects which it is not possible to anticipate such as stomach upset or nausea, headache, though these are rare. It is therefore important that you immediately notify one of the individuals listed below if you experience any unusual symptoms or have any concerns.

Confidentiality:

Personal records relating to this study will be kept confidential. Any research data collected about you during this study will not identify you by name, only by your initials and a coded number and kept for at least seven years. Your name will not be disclosed outside the research clinic. Any report published as a result of this study will not identify you by name.

For this study, the study doctor may need to access your personal health records for health information such as past medical history and test results. He/she may also need to contact your family physician and your other health care providers to obtain additional medical information. The health information collected as part of this study will be kept confidential unless release is required by law, and will be used only for the purpose of the research study. By signing the consent form you give permission to the study staff to access any personally identifiable health information which is under the custody of other health care professionals as deemed necessary for the conduct of the research.

The health information collected in this study will need to be checked from time to time against your medical records by representatives from the sponsoring drug company (name, if applicable). In addition to the investigators(s) and the sponsor representatives, the Health Research Ethics Board, the Health Products and Food Branch of Health Canada (if applicable), the United States Food and Drug Administration (if applicable), and/or other foreign regulatory agencies may have access to your records to monitor the research and verify the accuracy of study data.

By signing the consent form you give permission for the collection, use and disclosure of your medical records. In Canada, study information is required to be kept for 25 years. Even if you withdraw from the study, the medical information which is obtained from you for study purposes will not be destroyed. You have a right to check your health records and request changes if your personal information is incorrect.

Voluntary Participation:

You are free to withdraw from the study at any time, and your care in our clinic will not be affected in any way. If any knowledge gained from this or any other study becomes available which could influence your decision to continue in the study, you will be promptly informed.

Reimbursement of Expenses:

You will be reimbursed \$2.00 for each visit to cover incidental expenses such as parking.

Compensation for Injury:

If you become ill or injured as a result of participating in this study, necessary medical treatment will be available at no additional cost to you. By signing this consent form you are not releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

Contact Names and Telephone Numbers:

If you have concerns about your rights as a study participant, you may contact the Patient Relations Office of Capital Health, at 407-1040. This office has no affiliation with the study investigators.

Please contact any of the individuals identified below if you have any questions or concerns:

Name and Title:

Telephone Number:

Dr. Norman Thie Principal Investigator

(780) 492-9906 or (780) 492-2300

Dr. Michele Wilson Co-investigator

(780) 492-6895 or (780) 492-2300

At the start of the study, a pager number and name of the research assistant will be added to this information which will provide 24 hours a day contact.

2.8 Informed Consent



UNIVERSITY OF
ALBERTA

Department of Dentistry
Faculty of Medicine and Dentistry

Dentistry and Dental Hygiene - Excellence in Dental Health
Dentistry/Pharmacy Centre
Edmonton, Alberta, Canada T6G 2N8

CONSENT FORM

Part 1

Double-Blinded Randomized Clinical Study of Topical Diclofenac Efficacy versus Placebo in Symptomatic Relief of Temporomandibular Degenerative Joint Disease (TMDJD)

Principal Investigator:

Dr. Norman Thie

Co-Investigator:

Dr. Michele Wilson

Phone Number(s):

492-9906 or 492-2300

Phone Number(s):

492-6895 or 492-2300

Part 2 (to be completed by the research subject):

	<u>Yes</u>	<u>No</u>
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to withdraw from the study at any time, without having to give a reason and without affecting your future medical care?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your records, including personally identifiable health information?	☐	☐
Do you want the investigator(s) to inform your family doctor that you are participating in this research study? If so, give his/her name _____	☐	☐

Who explained this study to you? _____

I agree to take part in this study: YES ☐ NO ☐	
Signature of Research Subject _____	
(Printed Name) _____	
Date: _____	
Signature of Witness _____	
I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.	
Signature of Investigator or Designee _____ Date _____	
THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH SUBJECT	

2.9 Initial Screening Data Collection Sheet

Double-blind Randomized Clinical Study on Topical Diclofenac Gel Efficacy versus Placebo in Symptomatic Relief of Temporomandibular Degenerative Joint Disease (TMDJD)

INITIAL

CLINICAL SCREENING ASSESSMENT

Date: _____ (DD/MM/YR)

Patient Name: _____ Study No: _____

DOB: _____ (DD/MM/YR)

Family Physician Name _____

Chief complaint: _____

Onset: _____

Reported pain during function such as eating, talking, laughing and/or yawning: VAS ____

Prevalent Medical History:

Allergies: _____

Current Medications: _____

Screening Intraoral Examination:

Soft Tissue:

Salivary glands

Palate

Periodontal disease

Buccal mucosa

Gingiva

Tongue

Floor of mouth

Dentition:

Tooth decay Percussion sensitivity Dental infection

TMJ:

Right TMJ

Sounds

(Clicking, grating, popping, snapping)

Pain (VAS) _____

Left TMJ

Sounds

(Clicking, grating, popping, snapping)

Pain (VAS) _____

Range of Motion:

Voluntary Opening: _____ mm

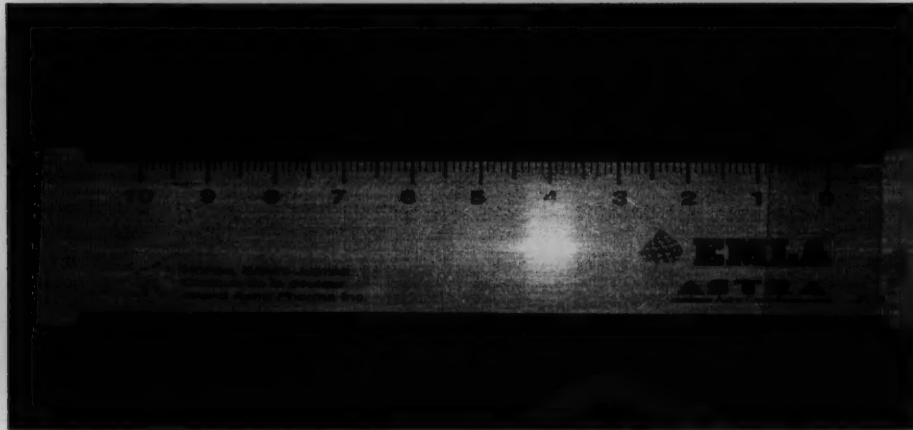
Assisted Opening: _____ mm

Self reported pain intensity (1 week average): VAS _____

Radiographic Results:

NOTES:

2.10 Visual Analogue Scale (VAS)



10

Worst imaginable pain

0

No pain

2.11 Authorization to Contact Family Physician



UNIVERSITY OF
ALBERTA

Department of Dentistry
Faculty of Medicine and Dentistry

Dentistry and Dental Hygiene - Excellence in Dental Health
Dentistry/Pharmacy Centre
Edmonton, Alberta, Canada T6G 2N8

PHYSICIAN'S CONSENTFORM

Title of Research Project:

**Double-blind Randomized Clinical Study on Topical Diclofenac Efficacy
in the Symptomatic Relief of Temporomandibular Degenerative Joint
Disease (TMDJD)**

Principal Investigator:

**Dr. Norman Thie,
Director of the TMD/Orofacial Pain Clinic**

Phone: (780) 492-2300

Fax: (780) 492-6451

Co-Investigator:

**Dr. Michele Wilson,
TMD/Orofacial Pain Clinic Resident**

Phone: (780) 492-2300

Or (780) 492-6895

I, _____, have been informed about the study
and I wish to be a participant. I have read the patient information and have had time to
discuss the study with Dr. Michele Wilson.

I give my permission for Dr. Michele Wilson to contact my family physician (MD'S name)
_____ for consent to continue in the study.

Date

Signature

I acknowledge that this patient, _____, qualifies for participation in
the above study. I acknowledge that I know the patient's clinical status and that there are
no medical contraindications or exclusion criteria to prohibit enrolling the patient.

Name of Physician

Signature

Date

2.12 Letter of Approval for Family Physician



UNIVERSITY OF
ALBERTA

Department of Dentistry
Faculty of Medicine and Dentistry

Dentistry and Dental Hygiene - Excellence in Dental Health
Dentistry/Pharmacy Centre
Edmonton, Alberta, Canada T6G 2N8

Dear Dr.

Under the supervision of Dr. Norman Thie, I am conducting a double blind study on the efficacy of topical diclofenac versus placebo in the symptomatic relief of temporomandibular degenerative joint disease as part of my requirements for my Masters in Medical Science.

The main objectives of this study is to see if topical diclofenac is effective in the reduction of pain and improve function of patients with temporomandibular degenerative joint disease and if there is an overall improvement of their quality of life as a result.

Inclusion Criteria:

1. A baseline score of ≥ 3.0 cm on a 10cm measured VAS (Visual Analogue Scale) according to the criteria established by Collins et al. (Collins, Moore, & Mcquay, 1997) (for moderate and severe pain) required for participants prior to use of analgesics, in order to provide adequate sensitivity.
2. Females from the ages of 18 to 45 years of age inclusive.
3. Primary degenerative joint disease as diagnosed through radiographs utilizing volumetric cone beam computed tomographic images reformatted in axial, coronal, and sagittal views that will be assessed by an independent radiologist.

The exclusion criteria of this study are as follows:

1. Nursing or expectant females or females planning on becoming pregnant.
2. Patients not clearly diagnosed as having symptomatic degenerative joint disease.
3. Patients having DJD secondarily to trauma, previous infection or general joint/muscle disease.
4. Patients who have experience adverse reactions to any of the components of the formulation used in the study.
5. Patients who have evidence of periodontal disease, dental caries, oral pathology or infections of the oral cavity.
6. Patients with a history of neuropathic pain in the orofacial region.
7. Patients scheduled for surgery in the near future.
8. Patients currently undergoing orthodontic treatment.
9. Patients with a history of epilepsy, cardiovascular disease, renal disease/disorder, hepatic disease/disorder, glaucoma, bowel obstruction, urinary retention, diabetes, hypertension or orthostatic hypotension.
10. Patients with a malignancy.

11. Patients who are currently using topical preparations for palliative relief for their DJD.
12. Patients with a baseline intensity of $\leq 3/10$ on the VAS.
13. Inability to understand English.
14. Patients who have been wearing an occlusal splint ≤ 3 months.

The study will involve a 10 day wash-out period for medications currently used prior to the start of this study. Acetaminophen will be provided to the patient for relief of breakthrough pain. The maximum per day will be 4000mg. No other medication for pain management may be used during the entire of time of the study including the wash-out period.

If the acetaminophen does not provide adequate relief during this study, the patient may withdraw from the study, at any time and no reasons have to be given.

Please find attached the consent to release information from your patient regarding their medical condition and approval to participate in our research project. Prior to the commencement of the study, we must receive documentation signed and approved by you. If there is any reason that this patient should not participate, please notify of such.

If you require additional information, please do not hesitate to contact me directly at 492-6895. Thank you for taking the time to peruse this information.

Sincerely,

Michele Wilson.B.Sc., D.D.S.
TMD/Orofacial Pain Resident

2.13 Pain Disability Index

The rating scales below are designed to measure the degree which several aspects of your life are presently disrupted by chronic pain. In other words, we would like to know how much your pain is preventing you from doing what you would normally do, or from doing it as well as you normally would. Respond to each category by indicating the overall impact of pain in your life, not just when the pain is at its worst.

For each of the seven categories of life activity listed, please circle the number on the scale which describes the level of disability you are typically experience. A score of 0 means no disability at all, and a score of 10 signifies that all of the activities in which you would normally be involved have been totally disrupted or prevented by your pain.

1. Family / Home Responsibilities. This category refers to activities related to the home or family. It includes chores and duties performed around the house (e.g., yard work) and errands or favors for other family members (e.g. driving the children to school).

0	1	2	3	4	5	6	7	8	9	10
no disability										total disability

2. Recreation. This category includes hobbies, sports, and other similar leisure time activities.

0	1	2	3	4	5	6	7	8	9	10
no disability										total disability

3. Social Activity. This category refers to activities which involve participation with friends and acquaintances other than family members. It includes parties, theater, concerts, dining out, and other social functions.

0	1	2	3	4	5	6	7	8	9	10
no disability										total disability

4. Occupation. This category refers to activities that are a part or directly related to one's job. This includes nonpaying jobs as well, such as that of a housewife or volunteer worker.

0	1	2	3	4	5	6	7	8	9	10
no disability										total disability

5. Sexual Behavior. This category refers to the frequency and quality of one's sex life.

0	1	2	3	4	5	6	7	8	9	10
no disability										total disability

6. Self care. This category includes activities which involve personal maintenance and independent daily living (e.g. taking a shower, driving, getting dressed, etc.).

0	1	2	3	4	5	6	7	8	9	10	
no disability											total disability

7. Life-Supported Activity. This category refers to basic life supporting behaviors such as eating, sleeping, and breathing.

0	1	2	3	4	5	6	7	8	9	10	
no disability											total disability

2.14 Short-Form Brief Pain Inventory (sf-BPI)


 Date: / /
 (month) (day) (year)

Study Name: _____
 Protocol #: _____
 PI: _____
 Revision: 07/01/05

Subject's Initials: _____
 Study Subject #:

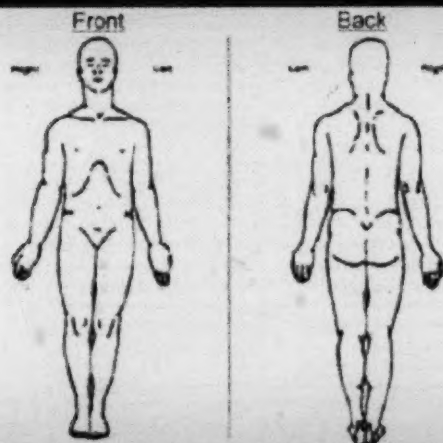
PLEASE USE
BLACK INK PEN

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
 No Pain Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its **least** in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
 No Pain Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the **average**.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
 No Pain Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have **right now**.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
 No Pain Pain As Bad As You Can Imagine

Subject's Initials :

Study Subject #:

Study Name: _____

Protocol #: _____

PI: _____

Revisão: 07/01/05

PLEASE USE
BLACK INK PEN

7. What treatments or medications are you receiving for your pain?

[illegible]

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much **relief** you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

☐ No Relief ☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with you:

A General Activity

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Does Not Completely
Interfere Interferes

B Mood

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Does Not Completely
Interfere Interferes

C. Walking ability

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Does Not Completely
Interfere Interferes

D Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Does Not Completely
Interfere Interfere

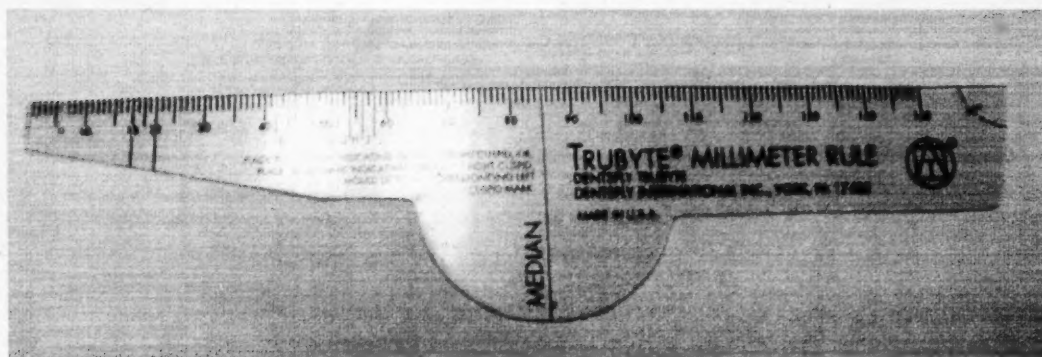
F Sleep

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Does Not Completely
Interfere Interferes

G. Enjoyment of life

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Does Not Completely
Interfere Interfere

2.15 Ruler (100mm)



2.16 Pairwise Comparison Table (VAS) (ITT)

Pairwise Comparisons

Measure: VAS

(I) factor1	(J) factor1	Mean Difference (I-J)	Std. Error	Sig.(a)	95% Confidence Interval for Difference(a)	
					Lower Bound	Upper Bound
1	2	1.012	.401	.110	-.137	2.162
	3	1.253	.447	.058	-.029	2.534
	4	1.661(*)	.445	.006	.387	2.935
2	1	-1.012	.401	.110	-2.162	.137
	3	.240	.306	1.000	-.637	1.117
	4	.648	.249	.092	-.066	1.363
3	1	-1.253	.447	.058	-2.534	.029
	2	-.240	.306	1.000	-1.117	.637
	4	.408	.272	.880	-.372	1.188
4	1	-1.661(*)	.445	.006	-2.935	-.387
	2	-.648	.249	.092	-1.363	.066
	3	-.408	.272	.880	-1.188	.372

Based on estimated marginal means

* The mean difference is significant at the .05 level.

a Adjustment for multiple comparisons: Bonferroni.

2.17 PubMed Literature Search

Using terms HRQL AND TMD resulted in one reference:

- 1: Jedel E, Carlsson J, Stener-Victorin E.
Health-related quality of life in child patients with temporomandibular disorder pain. Eur J Pain. 2007 Jul;11(5):557-63. Epub 2006 Aug 28.

Using terms assessment tools AND TMD resulted in 5 references:

- 1: de Lucena LB, Kosminsky M, da Costa LJ, de Góes PS. Validation of the Portuguese version of the RDC/TMD Axis II questionnaire. Braz Oral Res. 2006 Oct-Dec;20(4):312-7.
- 2: Reiter S, Eli I, Gavish A, Winocur E. Ethnic differences in temporomandibular disorders between Jewish and Arab populations in Israel according to RDC/TMD evaluation. J Orofac Pain. 2006 Winter;20(1):36-42.
- 3: Goldberg MB, Mock D, Ichise M, Proulx G, Gordon A, Shandling M, Tsai S, Tenenbaum HC. Neuropsychologic deficits and clinical features of posttraumatic temporomandibular disorders. J Orofac Pain. 1996 Spring;10(2):126-40.
- 4: Suzuki Y, Hinoshita H, Yokoyama K, Yamada A, Ogura Y, Mimura N, Yoshinaga H. [Histopathological assessment of renal biopsy specimens of subjects with urine abnormality] Nippon Jinzo Gakkai Shi. 1995 May;37(5):284-90. Japanese.
- 5: Braun B, Schiffman EL. The validity and predictive value of four assessment instruments for evaluation of the cervical and stomatognathic systems. J Craniomandib Disord. 1991 Fall;5(4):239-44.

Articles of the first two references were obtained and from them search terms such as pain assessment tools, RDC/TMD Axis II and Oral Health Impact Profile (OHIP) were noted. Using OHIP AND TMD revealed 9 articles with 8 of the articles assessing various forms of the OHIP with various oral health populations which included TMD.

- 1: Baba K, Igarashi Y. [The relationship between missing occlusal units and oral health-related quality of life in SDA patients] Nihon Hotetsu Shika Gakkai Zasshi. 2007 Oct;51(4):717-25. Japanese.
- 2: Hägglin C, Berggren U, Hakeberg M, Edvardsson A, Eriksson M. Evaluation of a Swedish version of the OHIP-14 among patients in general and specialist dental care. Swed Dent J. 2007;31(2):91-101.
- 3: Reissmann DR, John MT, Schierz O, Wassell RW. Functional and psychosocial impact related to specific temporomandibular disorder diagnoses. J Dent. 2007 Aug;35(8):643-50. Epub 2007 Jun 15.
- 4: John MT, Reissmann DR, Schierz O, Wassell RW. Oral health-related quality of life in patients with temporomandibular disorders. J Orofac Pain. 2007 Winter;21(1):46-54.
- 5: John MT, Miglioretti DL, LeResche L, Koepsell TD, Hujoel P, Micheelis W. German short forms of the Oral Health Impact Profile. Community Dent Oral Epidemiol. 2006 Aug;34(4):277-88.
- 6: Wolfart S, Heydecke G, Luthardt RG, Marré B, Freesmeyer WB, Stark H, Wöstmann B, Mundt T, Pospiech P, Jahn F, Gitt I, Schädler M, Aggstaller H, Talebpour F, Busche E, Bell M. Effects of prosthetic

treatment for shortened dental arches on oral health-related quality of life, self-reports of pain and jaw disability: results from the pilot-phase of a randomized multicentre trial. *J Oral Rehabil.* 2005 Nov;32(11):815-22.

7: Segù M, Collesano V, Lobbia S, Rezzani C. Cross-cultural validation of a short form of the Oral Health Impact Profile for temporomandibular disorders. *Community Dent Oral Epidemiol.* 2005 Apr;33(2):125-30.

8: Larsson P, List T, Lundström I, Marcusson A, Ohrbach R. Reliability and validity of a Swedish version of the Oral Health Impact Profile(OHIP-S). *Acta Odontol Scand.* 2004 Jun;62(3):147-52.

9: Segù M, Lobbia S, Canale C, Collesano V. [Quality of life in patients with temporomandibular disorders] *Minerva Stomatol.* 2003 Jun;52(6):279-87. Italian.

2.18 Data Collection Sheets

Double-blind Randomized Clinical Study on Topical Diclofenac Gel Efficacy versus Placebo in Symptomatic Relief of Temporomandibular Degenerative Joint Disease (TMDJD)

Data Collection Sheet: Day 0 (Baseline)

Date: _____ (DD/MM/YR)

Patient Name: _____ Study No: _____

DOB: _____ (DD/MM/YR)

Chief complaint: _____

Onset: _____

Clinical Examination:

Right TMJ

Sounds

(Clicking, grating, popping, snapping)

Left TMJ

Sounds

(Clicking, grating, popping, snapping)

Range of Motion:

Voluntary Opening: _____ mm

Assisted Opening: _____ mm

Pain: _____

Self reported pain intensity (1 week average): VAS _____

Reported pain during function such as eating, talking, laughing and/or yawning: VAS _____

Comments:

Next Visit:

Double-blind Randomized Clinical Study on Topical Diclofenac Gel Efficacy versus Placebo in Symptomatic Relief of Temporomandibular Degenerative Joint Disease (TMDJD)

Data Collection Sheet: Day 30

Date: _____ (DD/MM/YR)

Patient Name: _____ Study No: _____

DOB: _____ (DD/MM/YR)

Chief complaint: _____

Onset: _____

Clinical Examination:

Right TMJ

Sounds
(Clicking, grating, popping, snapping)

Left TMJ

Sounds
(Clicking, grating, popping, snapping)

Range of Motion:

Voluntary Opening: _____ mm

Assisted Opening: _____ mm

Pain:

Self reported pain intensity (1 week average): VAS _____

Reported pain during function such as eating, talking, laughing and/or yawning: VAS _____

Side Effects:

Application Site:

Dry skin
Paraesthesia
Burning
Urticaria
Pruritus
Vesiculobullous rash

Gastrointestinal (GI)

abdominal pain
constipation
diarrhea
nausea
vomiting
breathiness

Other

dizziness
edema
halitosis
headache
altered taste

Comments:

Next Visit:

Double-blind Randomized Clinical Study on Topical Diclofenac Gel Efficacy versus Placebo in Symptomatic Relief of Temporomandibular Degenerative Joint Disease (TMDJD)

Data Collection Sheet: Day 60

Date: _____ (DD/MM/YR)

Patient Name: _____ Study No: _____

DOB: _____ (DD/MM/YR)

Chief complaint: _____

Onset: _____

Clinical Examination:

Right TMJ

Sounds
(Clicking, grating, popping, snapping)

Left TMJ

Sounds
(Clicking, grating, popping, snapping)

Range of Motion:

Voluntary Opening: _____ mm

Assisted Opening: _____ mm

Pain:

Self reported pain intensity (1 week average): VAS _____

Reported pain during function such as eating, talking, laughing and/or yawning: VAS _____

Side Effects:

Application Site:

Dry skin
Paraesthesia
Burning
Urticaria
Pruritus
Vesiculobullous rash

Gastrointestinal (GI)

abdominal pain
constipation
diarrhea
nausea
vomiting
breathiness

Other

dizziness
edema
halitosis
headache
altered taste

Comments:

Next Visit:

Double-blind Randomized Clinical Study on Topical Diclofenac Gel Efficacy versus Placebo in Symptomatic Relief of Temporomandibular Degenerative Joint Disease (TMDJD)

Data Collection Sheet: Day 90

Date: _____ (DD/MM/YR)

Patient Name: _____ Study No: _____

DOB: _____ (DD/MM/YR)

Chief complaint: _____

Onset: _____

Clinical Examination:

Right TMJ

Sounds
(Clicking, grating, popping, snapping)

Left TMJ

Sounds
(Clicking, grating, popping, snapping)

Range of Motion:

Voluntary Opening: _____ mm

Assisted Opening: _____ mm

Pain:

Self reported pain intensity (1 week average): VAS _____

Reported pain during function such as eating, talking, laughing and/or yawning: VAS _____

Side Effects:

Application Site:

Gastrointestinal (GI)

Other

Dry skin
Paraesthesia
Burning
Urticaria
Pruritus
Vesiculobullous rash

abdominal pain
constipation
diarrhea
nausea
vomiting
breathiness

dizziness
edema
halitosis
headache
altered taste

Comments:

Next Visit:

2.19 Research Screening Imaging Summary

Double-blind Randomized Clinical Study on Topical Diclofenac Gel Efficacy versus Placebo in Symptomatic Relief of Temporomandibular Degenerative Joint Disease (TMDJD)

Screening of Potential Subjects for Dr. Michele Wilson Research Project

Subject's Name: _____

Date of Birth: _____

Images Taken Date: _____ Report Date: _____

IMAGING SUMMARY

Bony Changes – Condyles

	Right				Left			
	med	ctr	lat	AP	med	ctr	lat	AP
Sclerosis								
Flattening								
Erosions								
Osteophyte								
SBC								

Bony Changes – Glenoid Fossae

	Right				Left			
	med	ctr	lat	AP	med	ctr	lat	AP
Sclerosis								
Flattening								
Erosions								
Osteophyte								
SBC								

Bony Changes – Articular Eminences

Condylar Position @ ICP

	Right				Left			
	med	ctr	lat	AP	med	ctr	lat	AP
Sclerosis								
Flattening								
Erosions								
Sclerosis								
SBC								

0 = centered	1 = anterior	2 = posterior	3 = medial	4 = lateral
		Right	Left	
Corrected Sagittal Plane				
Corrected Frontal Plane				

Resultant Joint Space

0 = none 1=anterior	2 = posterior	3 = medial
	4 = lateral	5 = superior
	Right	Left
Corrected sagittal	Narrowed	
Plane	Widened	
Corrected frontal	Narrowed	
Plane	Widened	

Notes:

Presence of Degenerative Joint Disease:

Right TMJ

Left TMJ

Yes / No

Yes / No

Radiologist's Signature: _____